



Destruction of liver by arsenphenamine (very low power magnification). Liver cells have disappeared from many areas leaving only bile ducts, blood vessels and collapsed framework. Some islands of remaining liver cells show fresh necrosis (left insert); in most the cells are well preserved (right insert). Page 238.

# INTERNATIONAL CLINICS

*A Quarterly*

OF

ILLUSTRATED CLINICAL LECTURES AND  
ESPECIALLY PREPARED ORIGINAL ARTICLES

ON

TREATMENT, MEDICINE, SURGERY, NEUROLOGY, PÆDIATRICS, OBSTET-  
RICS, GYNÆCOLOGY, ORTHOPÆDICS, PATHOLOGY, DERMATOL-  
OLOGY, OPHTHALMOLOGY, OTOTOLOGY, RHINOLOGY,  
LARYNGOLOGY, HYGIENE, AND OTHER  
TOPICS OF INTEREST

BY LEADING MEMBERS OF THE MEDICAL PROFESSION  
THROUGHOUT THE WORLD

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VOLUME III. FORTY-THIRD SERIES, 1933

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SEP -8 1933.

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# Diseases of the Parathyroid Glands

## THE DIAGNOSIS OF PARATHYROID OVERFUNCTION\*

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THE relationship of a certain type of skeletal decalcification to an excessive supply of the product of parathyroid glands is a topic of current interest. The subject involves many fields of medicine and its allied sciences, and thus concerns many groups of specialists. The endocrinologist is faced with a new glandular dysfunction, the biochemist is intrigued by the accompanying abnormalities of the metabolism of calcium and phosphorus, the pathologist and the orthopedist are impressed by the curious disturbances of the skeleton, and the ingenuity of the surgeon is challenged by the difficulties connected with the operative treatment.

### HISTORIC CONSIDERATIONS

An historic review will help to orient the bone lesions involved, and to distinguish this affection from disturbances in the group of osteomalacic conditions. I shall be guided for a way in this by the recent monograph of Lièvre, which contains the most complete account of the clinical development of the subject that has been written up to the present.

"Parathyroid osteosis,"\*\* as Lièvre calls the disease, or "oste-

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\* One of three Colver Lectures, delivered at Los Angeles, California, November 15 to 17, 1932.

\*\* The term "parathyroid osteosis" is better than any thus far proposed. "Osteitis fibrosa cystica," which has heretofore been chiefly used in American literature, is far less satisfactory. The lesion is not inflammatory, other fibrous and cystic lesions of bone exist, and cysts are not obligatory in this one. The term adopted by the Congress of the German Anatomical Society, namely, "osteodystrophia fibrosa" fails to indicate the correlation with the hyperfunction of the parathyroid glands which is involved.

Submitted for publication December 31, 1932.

dystrophia fibrosa," according to the official German terminology, is a new disease only in the sense that the knowledge of its pathogenesis is new. The peculiar decalcification and unusual fragility and flexibility of the bones that accompany it must have been seen in Greece and Egypt and, according to Denninger, of the University of Chicago Archeological Survey, parathyroid osteosis existed in America in pre-Columbian times. The skeleton of a primitive American, recently discovered in a mound in northern Illinois, reveals lesions which have been interpreted as those of this condition.

In the past, however, no distinction was made between the various kinds of soft bones, and when the term "osteomalacia" was introduced by Duncan, early in the eighteenth century, the conditions were all called osteomalacia.

Lobstein, in 1833, introduced the term "fragilitas ossium" and included all cases in which there were fragile bones under that designation, not only cases of constitutional fragility, but others of metastatic carcinoma and some which undoubtedly were examples of the disease under consideration. The constitutional or familial fragilitas ossium, associated with bluish sclera and deafness, the syndrome of van der Hoeve, has been called Lobstein's disease.

The first anatomic description of the lesions in bone of parathyroid overfunction is attributed by Lièvre to Stansky, whose Paris thesis in 1839 was based on the observation of a case of what he called osteomalacia. The osseous tissues, in Stansky's description, "had almost completely disappeared from the tibia and the iliac bones, being replaced by a meaty substance of a red brown color, homogeneous in appearance, drenched in serosanguineous fluids and filling considerable cavities found in the degenerated mass. This was seen with the microscope to be deposited in the spongy tissue of the bone. . . . In the neck of the femur were cavities filled with a soft, pulposus, reddish substance, with scarcely a trace of fat."

A number of similar descriptions appeared in the next three decades, but especially important was the observation of giant cells by Robin in 1849 and by Kölliker in 1850, and the Paris thesis of Nélaton which contained a complete description of a giant cell tumor. Nélaton's observations were limited to epulis, and single giant cell tumors of the long bones, but, in an appendix to his thesis, he commented that giant cell tumors could be of wide distribution and sug-

gested, with rare intuition, that such tumors might be the cause of diffuse softening of the skeleton such as had been observed by Stansky.

Rindfleisch, in 1864, discovered osteoid tissue in osteomalacic bone and showed that osseous tissue containing no calcium stained deeply with carmine. This led to the error of considering every condition in which there was osteoid tissue as osteomalacia. In the same year a case of "cystic degeneration of the entire skeleton" was described by Engel, whose anatomic notes clearly indicate the presence of parathyroid osteosis.

Meanwhile Guérin and Trousseau, in 1865, were studying cases of puerperal osteomalacia, observing the beneficial effect in them of cod liver oil and maintaining the identity of osteomalacia and rickets. Their conclusion as to the identity of osteomalacia and rickets has been substantiated, but it applies only to a special form of what at that time was included under osteomalacia, and does not apply to the condition described by Stansky and Engel.

Paget, in 1877, called attention to a chronic inflammatory disease of bone that affected persons of middle age and old age, and which was characterized by thickening of the bones, and by bending. This "osteitis deformans" of Paget has been shown recently not to be associated with any abnormality of the parathyroid glands, nor with any disturbances of the metabolism of calcium. Spontaneous fractures in this condition are rare, and removal of parathyroid glands is without benefit; nevertheless, Paget's disease was confounded, in its turn, with parathyroid osteosis so that the two conditions were taken up as subtypes of a common fibrocystic osteitis in the publication of von Recklinghausen, in 1891, and are so regarded to this day by some writers.

Almost every author who has been writing recently on the subject of parathyroid overfunction has credited von Recklinghausen with the discovery of the bone lesions it produces, referring to the condition as von Recklinghausen's disease, but Lièvre considers that this is historically unjust. Typical cases were described, as has been stated, long before the appearance of von Recklinghausen's much quoted paper in Virchow's *Festschrift*, and in that paper von Recklinghausen confused the condition named for him with Paget's disease. The first part of the paper was devoted to "fibrous or deforming



osteitis"; six cases were reported, of which four were instances of Paget's disease and two of the osteodystrophy later called the "generalized osteitis fibrosa cystica of von Recklinghausen." In a second section were reports of six cases, one of which was possibly an instance of disease of the parathyroid glands. A distinction was drawn between osteitis fibrosa and osteomalacia, but Paget's disease and what von Recklinghausen called osteitis fibrosa were lumped together, and later, in 1910, von Recklinghausen explained that the two were varieties of the same disease. This, in the light of recent work, was wrong. Lièvre, however, credits von Recklinghausen with the first really valuable anatomic description of the morbid entity about which I am speaking.

Occasional cases continued to be reported, and, in 1904, von Haberer's comparative study of diffuse disease of bone, and localized or focal bone cysts, prompted von Mikulicz to set apart the cysts of youth and adolescence under the name of "osteodystrophia cystica juvenalis." The condition is not related in any way to parathyroid osteosis, although roentgenologically it may be difficult to distinguish one from the other, because multiple cysts may occur, and progression is often noted. There are no disturbances of calcium metabolism and no other symptoms of diseases of the parathyroid glands. As with the solitary bone cysts, also called "osteitis fibrosa," there seems to be no relation to the parathyroid glands.

It thus appears that, before Paget, all cases in which there were soft bones were diagnosed either osteomalacia or fragilitas ossium, that after Paget two major generalized diseases of bone were recognized, osteomalacia and osteitis deformans, and that the disease now under consideration was classed at times with osteomalacia and at other times with Paget's disease. Even as late as 1926 Christeller divided the hypocalcifications of bones into two categories, the first that of osteomalacia and rickets, the second, a category called osteitis fibrosa, in which diverse conditions were grouped, including the so-called osteitis fibrosa of von Recklinghausen and the osteitis deformans of Paget.

The relationship of decalcification to the parathyroid glands was first suspected by Askanazy, who discovered, by accident, a tumorous parathyroid gland of a patient affected with what Askanazy called osteitis deformans, but which his description clearly shows was parathyroid osteosis. His description is this: "To the left of the left lobe

of the thyroid is a tumor (4.5 x 2 x 2 cm.) which looks almost like a second left thyroid lobe. Histologically it is markedly different, consisting of narrow strands of cubical epithelium. Nowhere is there any colloid. One must think of parathyroid origin for this tumor." The calvarium could be compressed like thick rubber and thin sections of it could be cut with a razor. The pelvis was heart shaped. The femur was fractured in three places, the corticalis was thin and the spongiosa wide-meshed. Microscopically there was "an alteration of the deposition and destruction of bone. The process of destruction of old bone is carried out by numerous osteoclasts lying in Howship's lacunae. Sometimes one sees a small bony particle surrounded by giant cells and finally only the osteoclasts, single or in groups, free in connective tissue."\*

This was in 1904. The description identifies the disease I am concerned with, but the isolated observation, the significance of which was barely suspected, attracted no attention, and confusion was soon created by the discovery of Erdheim that the parathyroid glands might also be enlarged in osteomalacia and rickets. In 1925, Hoffheinz reviewed from the literature forty-five cases of hypertrophied parathyroid glands, twenty-seven associated with disease of bone, including seventeen of generalized fibrous osteodystrophy, eight of osteomalacia and two of rickets, and Erdheim's view that hypertrophy of the parathyroid glands in osteomalacia was a secondary and compensating phenomenon was taken by other investigators to apply generally to several other diseases of bone. This hypothesis is probably correct if limited to osteomalacia and rickets; it is incorrect, as subsequent developments proved, when applied to the tumor-like hypertrophy of the parathyroid glands found in association with parathyroid osteosis. Additional difficulties of interpretation were introduced by reports of fibrous changes in bone without tumors of the parathyroid glands and by the occasional occurrence of tumors in cases without lesions of bone or other symptoms.

The development of the knowledge of the physiology of the parathyroid glands should be considered briefly. These glands, also known as epithelial bodies, were first described in 1880 by Sandström, but no great attention was paid to them until Gley, in 1890, presented evidence that tetany was produced in rabbits by what he

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\* Translation from Donald Hunter's Goulstonian lecture.

termed "complete thyroidectomy." Between 1896 and 1900 Vassalle and Generali, and Moussu demonstrated the functional independence of parathyroid glands and the thyroid gland, and showed that the absence of the former was the cause of the tetany that followed the combined resection of the thyroid gland and the parathyroid glands. The successful transplanting of parathyroid tissue, and the relief of tetany thereby, reported by Halsted and others, marked a further advance. However, because extracts of the hormone of the parathyroid glands could not be obtained, an erroneous hypothesis was developed by which the action of the glands was described as one of detoxication. The idea was based on finding increased quantities of guanidine in the urine in parathyroidectomized dogs (Koch), and the production of symptoms of tetany on injection of guanidine (Paton and Finley). It was also shown that parathyroidectomized animals would remain free from tetany if they were fed exclusively on milk (Dragstedt) and that flushing the blood stream with large quantities of fluids would relieve the tetany of animals after parathyroidectomy (Luckhardt). These measures were presumed to limit and diminish respectively the amount of toxic amines in the blood.

In the meantime Parhon and Urechie and MacCallum and Voegtlin had discovered that giving calcium would correct the spasms of parathyroid tetany, and in 1913 MacCallum and Vogel demonstrated by direct analysis that the blood in cases of tetany contained less calcium than in normal cases, thus placing the parathyroid glands in a commanding position so far as calcium metabolism was concerned. Finally, in 1923 and 1924, Hanson, and Collip working independently, secured active extracts of parathyroid glands and the theory of internal secretion was established. It was found by Collip, Aub, Hunter and others that parathormone, when injected into normal animals or man, would elevate the calcium of the blood while at the same time it depressed the phosphorus and induced an increased excretion of both phosphorus and calcium.

This then was the situation in 1926, when Mandl, of Vienna, performed the first resection of a parathyroid adenoma in a case of parathyroid osteosis, and not only cured the patient, but observed an almost immediate effect on the previously excessive excretion of calcium in the urine. His only rivals for the honor of originality are Schlagenhauser and Weil. The former, in 1915, apropos of two

cases of this disease, in which tumorous parathyroid glands were found at necropsy, questioned Erdheim's hypothesis as to the compensatory character of enlarged parathyroid glands, and recommended, in advanced cases, exploration and the removal of tumors if found. Weil, in 1922, treated a case of generalized osteitis by radio-therapy of the neck, and obtained what he reported as a remarkable result.

Mandl at first was influenced by Erdheim's views to treat his patient by implanting grafts of fresh parathyroid glands from man. As this method failed, Mandl put Schlagenhauser's suggestion to trial, and obtained his capital success. Others were quick to follow him: Gold, in Vienna, in 1927; Barrenschcen and Gold, in 1928; Beck, in Kiel, in 1928; Snapper, in Amsterdam, and Hunter, in London, in 1929. The first case reported in America was that of Barr and his associates in 1929; the second was one I reported in the same year and the third, the case of Boyd, Milgram and Stearns, also reported in that year. Richardson's case, described in 1929, was studied by DuBois and correctly diagnosed in the interval between the appearance of Mandl's first paper on the subject and that of Gold. The patient was bedridden and had lost 17.5 cm. in stature. The blood calcium was abnormally elevated and a negative calcium balance was demonstrated.

In spite of the very considerable benefit that had resulted from operation in all of these cases, except that of Barrenschcen, in which no tumor was found, and although these surgical results constituted an experimental refutation of Erdheim's view, as applied to the so-called osteitis fibrosa, doubt remained in some minds as to the exact relationship of the parathyroid tumors and the skeletal lesions, and much confusion existed as to what diseases of bone were concerned. Negative calcium balance and elevated blood calcium were found in association with other diseases in which bones were affected, such as multiple myeloma and metastatic carcinoma, and enlarged parathyroid glands were reported, as has been related, in osteomalacia and rickets.

Fortunately proof could be obtained and was soon brought to show that generalized fibrous osteodystrophy results from an excessive supply of the parathyroid hormone. Jaffe, Blair and Bodansky, in New York, and independently my pupil, J. L. Johnson, in Chicago, were able to reproduce the typical skeletal deformities of osteitis

fibrosa by long-continued injections of parathormone. Puppies and guinea pigs were used by Jaffe, Blair and Bodansky, and white rats and puppies by Johnson; in all cases, when properly adjusted doses of the extract were chosen, decalcification was obtained, with fibrous replacement, giant cells and cysts, characteristic of the clinical disorder described by Stansky, Nélaton, Engel, and von Recklinghausen.

Johnson's study was supplemented by experiments on metabolism conducted on two normal human beings, who received daily doses of 30 and 50 units, respectively, of parathormone. The biochemic and symptomatic reactions obtained were similar to those in the so-called von Recklinghausen's disease. The value for serum calcium rose, that for phosphorus fell, the metabolic balances for calcium and phosphorus were negative, and characteristic hypotonia, muscular and mental fatigue and tenderness of bone resulted.

Johnson also found an answer to the question of the relationship of osteitis fibrosa to the other skeletal diseases with which it had been confounded. He gave viosterol to one series of his animals, both before and during the administration of parathormone, without any inhibiting effect on the course of the disease and even some intensification of it. This result, which has been confirmed by Jaffe and his associates, proves most conclusively that the condition produced by an excess of parathyroid hormone is something radically different from osteomalacia and rickets. And the fact that, in all of the many experiments of Jaffe, and in those of Johnson, lesions were never seen, except those characteristic of parathyroid osteosis, is strong evidence that parathyroid overfunction produces this disease and no other; certainly not Paget's disease or osteomalacia, or multiple myeloma.

The hypertrophy of the parathyroid glands that accompanies osteomalacia, as noted first by Erdheim, and the similar hypertrophy of these glands that has been produced experimentally in fowls by deprivation of vitamin D, may well be an attempt at compensation, just as was originally suggested by Erdheim. That such enlarged glands produce more hormone than normal is not improbable, but if they do so there must exist an increased demand which the extra supply of hormone does not exceed. In parathyroid osteosis, there is a supply in excess of demand, for which a primary enlargement of parathyroid glands is responsible. In rickets and osteomalacia, hypertrophy involves all the parathyroid glands with more or less uni-

formity; in parathyroid osteosis, one gland, or at most two, are tumorous, whereas the remainder are normal in size and structure.

Hyperfunction of the parathyroid glands may occur in the absence of hypertrophy, as is suggested by some of the clinical cases now on record, and undoubtedly tumors of these glands occur without hyperfunction. Perfect analogies for both of these possibilities exist in the case of the thyroid gland, but claims that multiple diseases of the bone, such as arthritis and Paget's disease and myeloma, are due to an oversupply of parathyroid hormone, claims actually advanced by some of the surgical enthusiasts that have entered this field, should be met with the most profound skepticism.

#### SYMPTOMS

When the symptoms of this disease are well developed they constitute an unmistakable clinical syndrome. Pains of the bones, bending of the bones of the legs, shortening of the stature, and occasionally pathologic fractures or the development of bony tumors, are major osseous abnormalities. The weakness of the muscles is severe and their lack of tonus may be extreme. The electric excitability of the muscles is usually reduced. Visceral disturbances occur with more or less frequency, particularly renal colic from stones, vomiting, constipation or diarrhea, anorexia, and tachycardia.

The laboratories add further data. The roentgenograms of the bones are more or less diagnostic; in addition to generalized decalcification of a miliary or granular appearance, there is irregular thinning of the cortexes of the shafts of the long bones, a coarser trabeculation, especially noticeable in the vertebrae and the bones of the pelvis, stippled mottling of the calvarium, with some slight thickening and blurring of the inner and outer tables. In addition, multiple cysts may be seen and areas of erosion immediately underneath the periosteum, as noted first by Camp and Ochsner.

The abnormalities of metabolism are also striking in most cases. The concentration of calcium in the serum is usually elevated, and may even exceed 20 mg. for each 100 cc., as in a case described by Snapper. Elevations to 14 or 16 mg. for each 100 cc. of serum are not uncommon, in contrast to the normal values for calcium of 10 to 12 mg. The phosphorus of the serum is usually lowered to something less than 3 mg. for each 100 cc., whereas the normal range is from 3 to 5 mg., and the output of both calcium and phos-

phorus is increased, especially by an excessive amount of calcium in the urine. A negative balance for calcium may be found which amounts to 0.5 Gm. or more each day. The significance of this degree of calcium deficit was emphasized by Magnus-Levy who pointed out that 1 Gm. of calcium represents 4 Gm. of fresh compact bone and, not counting the organic watery part of the skeleton, a daily loss of 0.5 Gm. of calcium a day would mean an annual loss of 720 Gm. of bone, or one-fifth of the entire skeleton.

A good deal of emphasis has been placed recently on the phosphatase activity of the plasma. A method for estimating this was published by Kay, who expressed the phosphatase value in terms of the number of milligrams of phosphorus which will be liberated in forty-eight hours as inorganic phosphate on the addition of an excess of sodium B-glycerophosphate to 1 cc. of plasma. The temperature and pH must be held constant. The average value for normal plasma is 0.15 mg., but in almost all generalized diseases of the bone it is increased to many times this value, and in parathyroid osteosis it is always high.

Tumorous parathyroid glands often may not be felt in the neck, and when they are palpable it is impossible to distinguish them from adenomas of the thyroid gland. In the case, which I described in 1929, the palpable tumor was first thought to be an adenoma of the thyroid gland, whereas in the patient whose case was reported by Compere, and whom I also saw, a mass could be felt on one side of the neck, which at operation proved not to be a parathyroid tumor but an adenoma of the thyroid gland, and the tumor of the parathyroid gland was found lying deeply in the tissues of the opposite side.

The important features of the technic of operation in these cases have been pointed out in the surgical reports of Walton, Pemberton, and others. It is essential to explore the neck thoroughly and deeply, as otherwise small tumors can readily be missed, and also it is essential to look for more than one tumor, because multiple tumors are occasionally found. Thyroidectomy done at the time of operation is advisable, unless the thyroid gland is small and homogeneous, because a tumor of the parathyroid gland may be found buried in the substance of the thyroid tissue. The normal position of the parathyroid glands is in the groove between the esophagus and trachea, but misplacement of these organs is almost a rule, and the tumors may be found behind the trachea or behind the esophagus, in the preverte-

bral space. In one of Hunter's cases, in which Walton performed the operation, a soft, fleshy mass measuring 7.5 by 5 cm. was removed from in front of the second thoracic vertebra, behind the esophagus.

Removal of these tumors is followed, in a few hours, by significant readjustments in metabolism. The previously excessive excretion of calcium is counteracted to such a degree that almost no urinary calcium may remain, and the blood calcium falls to such low levels that symptoms of tetany present themselves. This reaction occurs so constantly after operation that, if it fails to develop, one should suspect that all of the tumorous parathyroid tissue has not been removed.

#### DIAGNOSIS

The diagnosis of parathyroid osteosis is comparatively easy to make if the disease is fully developed and well advanced; it offers serious difficulties in the early stages, and even some cases of several years' duration present puzzling problems. I reported one of these last month, with Camp, Robertson and Adams. The diagnosis was made with difficulty, and not until the patient had arrived at such a serious state of asthenia that she failed to survive operation, yet certain symptoms had been present for years. The patient had been nervous for seven years; prior to then she had been well. She had had stiff knees for three years and pain in the spine for two years, which confined her to her bed. The roentgenograms of the skull disclosed a diffuse granular type of osteoporosis and some thickening in the frontal and parietal regions; the vertebrae exhibited diffuse osteoporosis, and the intervertebral spaces were increased in width. Parathyroid osteosis was considered, but this diagnosis was rejected and a metastatic malignant condition of the bones was thought to be more probable. Later a pathologic fracture of the femur occurred, and at a second examination, twenty months later, there was no mistaking the condition. Exploration was done on the neck, and a parathyroid tumor was found and removed. The immediate response to operation was satisfactory, but at the end of the third week a gastro-intestinal complication occurred which ultimately led to the patient's death.

A permanent cure might have been obtained in this case had the patient received surgical treatment at her first visit. But, on the other hand, in three other cases with similar atypical features opera-



tion was performed and a tumor was not found. In another case with lesions more typical of parathyroid osteosis, exploration was similarly without result, but in this case it is possible that a tumor was overlooked.

The results of operation in three of our four cases with tumor have been quite satisfactory; the fourth case is the one just described at some length. The results of resection of nontumorous parathyroid glands, in the three atypical cases referred to, have been disappointing.

The differential diagnosis in hyperparathyroidism must take into account all other diseases in which the bones are involved, as well as a variety of visceral conditions.

Arthritis is scarcely to be confused with parathyroid osteosis, even though stiffness of the joints has been an early symptom in some cases, and although sometimes, owing to the decalcification of the surfaces, the joints may collapse and imitate destructive arthritis. The values for calcium in the blood have been reported by some investigators to be high in arthritis, and on this slim foundation enthusiasts have rushed to the conclusion that this disease was of parathyroid origin and that parathyroidectomy should be done.

Necessary as it is to have knowledge of the value for serum calcium in cases of parathyroid osteosis, one cannot base a diagnosis on this alone. The value for serum calcium has been found to be normal in some cases of unquestionable parathyroid overfunction, and on the other hand, hypercalcemia is observed in a variety of diseases in which there is no good reason to suspect the parathyroid glands. Opinion as to the value for calcium in arthritis is divided; Hench, Nachlas, and others with wide experience, have not encountered hypercalcemia in arthritis. It occurs at times in gout and leukemia, and especially in multiple myeloma and in cases of malignant tumor of the skeleton. Also, the calcium balance may be negative in any extensive destructive process involving the bone, such as multiple myeloma, endothelioma, or carcinoma of the bones, and similarly metastatic calcification in the kidneys, stomach and lungs, such as has been noted with considerable frequency in hyperparathyroidism, is found in these other decalcifying diseases. None of these abnormalities of metabolism is therefore diagnostic of parathyroid osteosis, and it is a mistake to place too much emphasis on them. The values for inorganic phosphorus of the serum are

probably more significant from a diagnostic standpoint than those for calcium. The value for serum phosphorus is usually low in hyperparathyroidism, whereas in multiple myeloma it is normal or high, according to Snapper, and Magnus-Levy.

Various diseases involving bone, which much be distinguished from parathyroid osteosis, include the following.

So-called osteitis cystica, also described by von Recklinghausen, is characterized by a solitary cyst or by multiple cysts, often filled with fibrous tissue containing giant cells, and is not to be distinguished histologically from the cysts in parathyroid osteosis. The condition, however, is sharply localized, and the adjacent parts of the skeleton appear normal. A closely related abnormality is the essential cyst of youth called osteodystrophia cystica juvenalis by von Mikulicz. The absence of all subjective symptoms in such cases, as well as the normal values for calcium and phosphorus in serum and urine, and the normal serum phosphatase distinguished them sharply.

Forms of endochondroma, usually localized in the bones of the hands and feet, are seldom confusing, but they occasionally affect multiple bones and then may offer difficulties. The significant differential criteria are that in endochondromas the unaffected portions of the skeleton are normal, and that when hyperparathyroidism has advanced to the point at which such a multiplicity of cysts is evident, the subjective symptoms, pain and asthenia, are extreme and the diagnosis is evident.

Schüller-Christian's syndrome of xanthomas of the membranous bones, exophthalmos, and diabetes insipidus is usually recognizable by the associated exophthalmos and diabetes. The associated exophthalmos and diabetes may be absent, however, and the xanthomatous lesions at times affect multiple bones, thus presenting difficulties. However, the bone surrounding the xanthomatous accumulations is not decalcified, as in parathyroid osteosis, and the roentgenographic pictures are therefore quite different.

Multiple myeloma and other malignant tumors of bones may produce clinical pictures that resemble those of parathyroid osteosis. As mentioned before, the value for calcium of the blood may be elevated, and the calcium balance negative. Pathologic fractures occur and the roentgenograms of the bones are not easily interpreted. There is, however, a real difference in the roentgenograms between these lesions and those of parathyroid osteosis, in that the bone adjacent

to each individual lesion is not affected in tumors, whereas there is general decalcification, at least in the more advanced cases of hyperparathyroidism. The frequent occurrence in the urine of Bence-Jones protein in multiple myeloma, establishes, when present, that this condition is not parathyroid osteosis.

The diagnosis of sarcoma has been made in a number of cases of parathyroid osteosis. The pain in the bones may be extreme in both conditions, and tissue obtained by biopsy in diseases of the parathyroid glands has been erroneously diagnosed as myelosarcoma on account of the presence of the giant cells. Ewing's sarcoma, when multiple bones are involved, might occasionally be mistaken for parathyroid osteosis, but should be distinguished by careful roentgenographic studies.

Paget's disease bears only a superficial resemblance, either clinically or roentgenologically, to parathyroid osteosis, and the calcium metabolism, as I have stated previously, is not disturbed at all. The value for phosphatase, however, is elevated in Paget's disease.

Osteomalacia and rickets usually can be diagnosed by the clinical history of deficient nutrition. They are characterized by normal or low values for serum calcium and normal or higher than normal serum phosphorus in contrast to conditions in parathyroid osteosis. The roentgenographic findings are also different. The rarefaction of the bones is much more homogeneous in osteomalacia and the miliary or granular appearance of parathyroid osteosis, as well as cysts and subperiosteal erosion, are missing. Osteoporosis of senility or dysfunction, and constitutional fragilitas ossium present no serious problems. The rarefaction of the bones is homogeneous in them, not patchy, as in parathyroid osteosis.

None of the conditions mentioned offers such difficult diagnostic problems to the thorough examiner, as does the recognition of hyperparathyroidism in its earlier stages, before a gross skeletal lesion has resulted. Symptoms are present, but their meaning is obscure: aching muscles, lassitude, mental and physical fatigue, nervousness, tachycardia, loss of appetite, constipation, sometimes diarrhea, rarely renal colic. Yet this is when the making of a diagnosis would be most beneficial. It occurred to me recently that determinations of the inorganic phosphates of the blood, together with the phosphatase, if obtained more or less as a routine in all cases in which this vague syndrome is present, might help to identify some early cases, but

such laboratory investigation of the large group of patients who may present such symptoms is hardly practicable. It is to be hoped that a more specific diagnostic criterion, either laboratory or clinical, will be developed in the future.

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# HYPERPARATHYROIDISM\*

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For a long time it has been the custom of our lay friends to poke fun at the medical profession for lack of progress in the treatment of disease. I can recall a good many occasions upon which it has been my fortune to be the central focus for this good natured banter.

Today, I am about to show you a patient with a medical condition about which we had scarcely any information ten years ago. I shall endeavor to bring out for you not only that medicine does make progress, but that it makes steady progress in the cause and cure of disease. I shall also try to show you from what sources our information is drawn and how knowledge obtained in some apparently unrelated field is applied by physicians to their problems.

Case—A. L. #48736, a twenty year old girl, was first admitted to the Strong Memorial Hospital on June 25, 1931. In March 1931, she had slipped on the ice sustaining a hard fall. This resulted in a fracture of the right humerus. It was treated by splinting. Two months following the injury there was still loss of motion in the shoulder and some weakness. Roentgen rays taken at this time gave evidence of a pathological fracture. Films of other bones showed lesions in the pelvis, skull, and right maxilla. She was sent to the hospital for roentgen ray therapy with a tentative diagnosis of myeloma. In her past history she had scarlet fever at seven years of age but otherwise had enjoyed good health. Examination showed a healthy appearing girl with no evident discomfort. There was a slight general fulness over the thyroid but it could not be palpated. The rest of the examination was normal with the exception of limitation in abduction of the right humerus at the site of the fracture. The roentgen rays showed areas of decreased density in the greater tuberosity of the right humerus with thinning of the outlines of these areas. The fracture line had crossed the shaft. The fracture was rounded and smooth with some periosteal proliferation. There was a considerable area of increased density, with some loss of the cortical appearance is typical of the left ilium and right femur.

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involved (Fig. 2). There was a cystic area in the left mandible. The diagnosis of multiple osteitis fibrosa cystica was made. The patient was sent into Dr. W. S. McCann's metabolism unit for a study of the calcium balance. A carefully controlled dietary regime was instituted under the direction of Dr. Samuel H. Bassett. The intake and output of calcium and phosphorus was analyzed. The patient was studied in twenty-nine test periods of six days each, variations in diet and drug therapy being introduced. During this whole time, however, the striking characteristics of the chemical studies on the blood were the following. There was a persistently high calcium in the blood, the readings being from 1 to 4 mg. above the normal. The blood phosphorus on the other hand, registered regularly 1 to 1.5 mg. below the normal level,—except when large doses of acid sodium phosphate caused a rise to normal. When this drug was administered the serum calcium also dropped more nearly to its normal level. During the study the patient was in positive calcium balance, i. e. the intake of calcium was in excess of the output except at one time when she was placed purposely on a low calcium and phosphorus diet. During this test period there was a negative calcium balance, in other words she excreted more calcium than she ingested (Fig. 3). These studies will be published in detail by Dr. Samuel H. Bassett. It was hoped that on high calcium intake she might repair her bone cysts without operation. Roentgen rays taken during her hospitalization showed that there were many cysts scattered over the whole skeleton. An enumeration of these cysts will be given but the time that they were first noted will not be included. She showed cystic areas in the skull; in the maxilla; in the upper end of the left humerus; in the upper end of the right humerus; in the external condyle of the right humerus; in the lower end of the right radius (Fig. 4); in the lower axillary border of the left scapula (Fig. 5); in the outer ends of the right 10th and 11th ribs (Fig. 6); in the pedicle of the 5th lumbar vertebra; in both rami of the pubis; in both wings of the ilium; in the lower ends of both femurs (Fig. 7); in the upper end of the right fibula (Fig. 8); in the lower end of the right tibia (Fig. 8); in the lower third of the left tibia,—two areas (Fig. 8); and in the scaphoid of the left foot. Besides this there was a general washing out of calcium apparent on examination of any of the bones. Some of the smaller cysts healed while under observation but others formed at the same time. (Fig. 8) It finally became apparent that a definite healing could by no means be predicted under medical treatment. Accordingly, an exploratory operation was performed on January 30, 1933. A nodule which measured 2.1 cm. by 1.8 cm. by 1.5 cm., weighing 1.3 Gm. was removed from under the right clavicle below the lower pole of the right thyroid lobe. This tumor was loosely attached to the capsule of the thyroid by a thin areolar tissue. It received its blood supply through a branch of the inferior thyroid artery. (Fig. 9) The tumor was about the color of parboiled liver. Exploration of the rest of the parathyroid regions on both sides showed nothing abnormal. The patient made a good recovery from operation. Viosterol which had been given in doses of 40 drops daily for three days before operation, was continued. The level of the blood calcium began to fall the day following removal of the tumor. On the second postoperative day she had numbness and tinglings of the hands, the arms and legs felt heavy, and she was quite depressed. Chvostek's sign was positive. The serum calcium fell to below the normal line. The serum phosphorus began to rise, and by the third day after operation was above its normal level. She continued to have latent tetany which could best be brought out in the morning before breakfast

when the serum calcium was lowest. During the day on high calcium diet and viosterol the serum calcium rose to almost the normal level and all signs of tetany disappeared. Improvement was rapid although she had symptoms of latent tetany, such as numbness in the finger tips, tingling in the lips, and "heavy sensations" in both legs for as long as three weeks after operation. She was discharged from the hospital one month after operation with no complaints.

Microscopic sections showed that the tumor was composed for the most part of large cells with a clear cytoplasm and large oval nuclei. These cells were about twice the size of normal parathyroid cells. There were thin interlacing strands of fibrous tissue throughout the section. About the periphery, there were cells of a cuboidal type with large dark staining nuclei. These cells were arranged in cords and in acini. In some of the acinar forms there was a colloid-like material in the lumen. Mitotic figures were not conspicuous. A diagnosis of adenoma of the right inferior parathyroid gland was made. (Figs. 10 and 11.)

I shall never forget the first instance of this disease which came to my attention. It was an advanced form of osteitis fibrosa cystica with generalized involvement of the whole skeleton. I was much interested in the clinical picture and was tempted to make a search of the literature for other similar cases. In 1922, I published a paper on "The Generalized Type of Osteitis Fibrosa Cystica,"<sup>1</sup> with a review of all the cases recorded in the literature to that time. I shall now read you a few sentences from that paper—"There can be no question that there is some fundamental change in the calcium metabolism of these cases. It would be interesting to know whether the calcium salts were retained in high concentration in the blood and excreted more rapidly than in the normal, analogous to the sugar changes in diabetes mellitus." This speculation has since that time been demonstrated to be the truth. There is a fundamental change in the calcium metabolism of these cases, and the comparison with the blood changes in diabetes mellitus also holds. In this latter disease a *deficient* production of an internal secretion results in an elevation of the blood sugar; whereas, in generalized osteitis fibrosa cystica an *increased* production of an internal secretion causes a rise of the serum calcium. In both conditions there is loss of the involved substances through the kidneys.<sup>2</sup>

The association of parathyroid gland enlargements with multiple cystic disease of the bones was noted as early as 1904 by Askanazy.<sup>3</sup> Erdheim<sup>4</sup> reported three such instances in 1907. He raised the question as to whether the enlargement of the parathyroid was primary or secondary and decided that it was an hypertrophy in response to a calcium deficiency in the skeleton. Scattered observations appeared in the literature from time to time but the recognition

FIG. 1.



Cystic area in upper end of humerus. Fracture line with healing is evident. The roentgen ray appearance of the cystic area in the external condyle of the lower end of the humerus is quite characteristic.

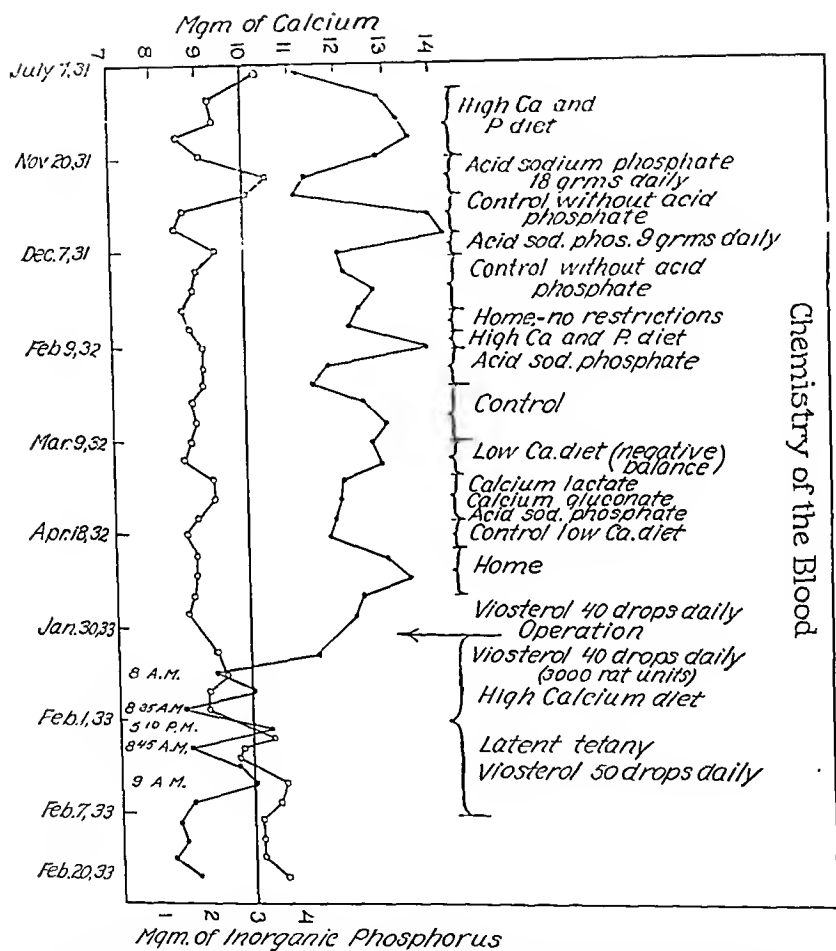


FIG. 2.



Cystic areas in the pubic rami and in the left ilium near the sacro-iliac joint.

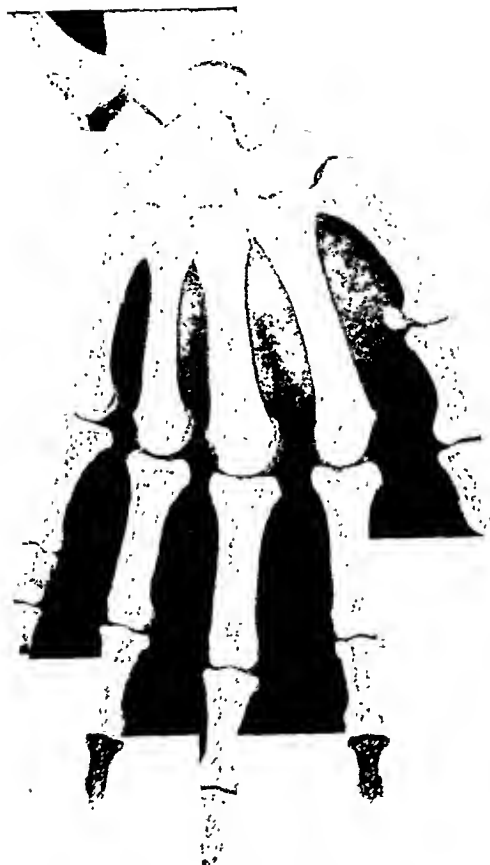
FIG. 3.



The figures for blood calcium (solid dots) were consistently above the normal line until after operation; whereas the figures for blood phosphorus were always below the normal until after operation. There was then a reversal.



FIG. 4.



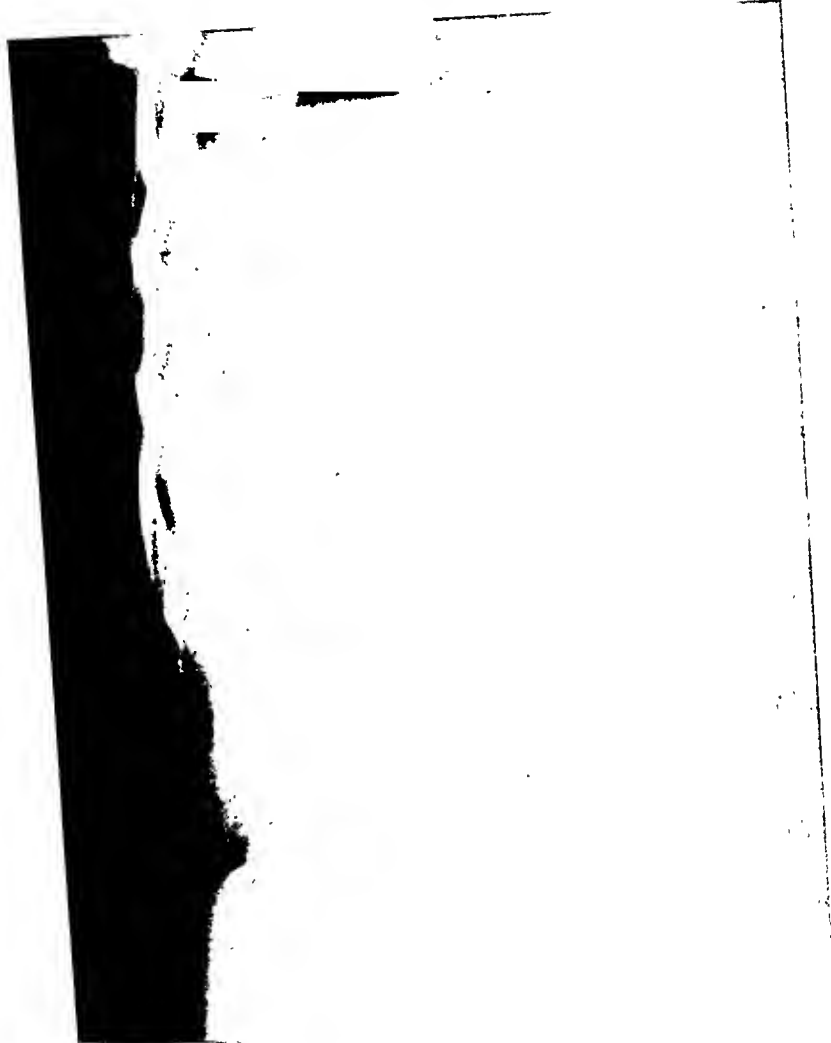
Characteristic cystic spaces in the lower end of the radius.

FIG. 5.



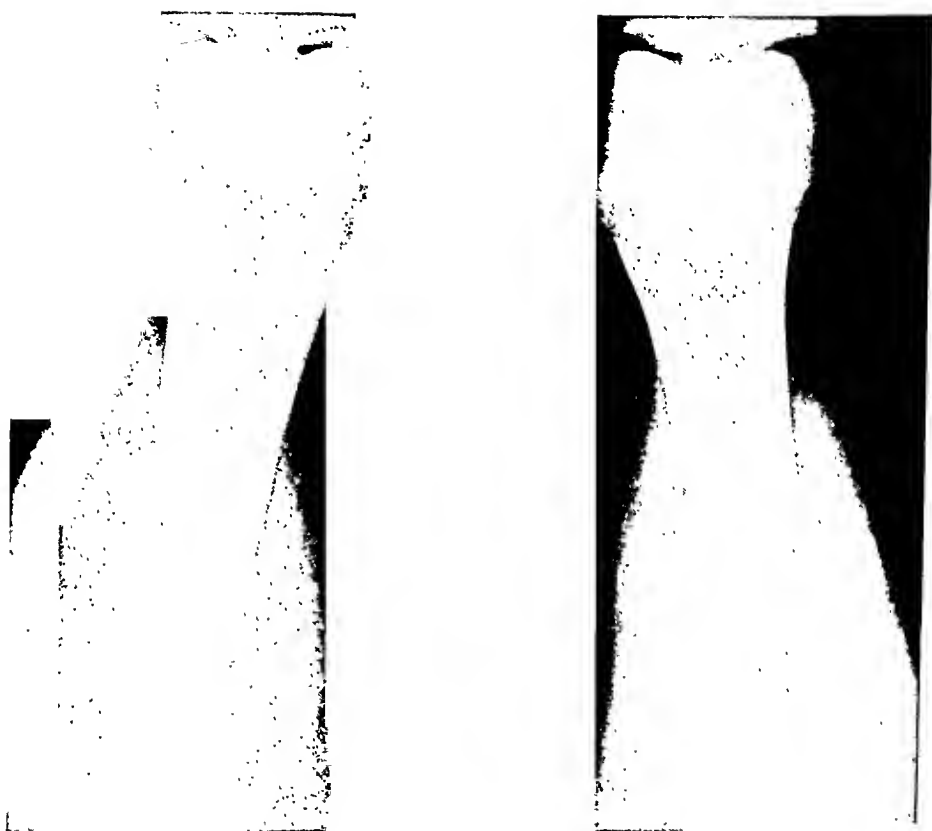
Cysts in the scapula-axillary border.

FIG. 6.



Cysts in the 10th and 11th ribs.

FIG. 7.



Cysts in both femurs—lower ends juxta-epiphyseal.

of the disease entity did not come about until the discovery of the parathyroid enzyme.<sup>5, 6</sup> When the properties of parathormone were determined by experiment, it became apparent that there was a relation between this glandular secretion and calcium withdrawal from the skeleton.<sup>7, 8, 9, 10</sup> Mandl<sup>11</sup> was the first surgeon to deliberately explore the parathyroid region for a suspected tumor in a case of multiple fibrocytic disease of bone. This was in 1926. Following his successful operation there have been to date probably about forty operations performed during which one or more enlarged parathyroid glands have been removed in cases of a similar nature.

The calcium metabolism has been studied for some time but great strides forward have come only in the last ten years. It was known from the work of MacCallum and Voegtlin<sup>12</sup> that removal of the parathyroids caused a marked reduction of the serum calcium in dogs and brought about a severe tetany. In the study of rickets by numerous investigators<sup>13, 14</sup> it has been established that there are several factors of prime importance in the proper calcification of bone. If the diet is high in calcium salts but poor in phosphorus under proper conditions rickets will result in experimental animals. If the diet is poor in calcium salts but high in phosphorus, a picture similar to rickets but complicated by tetany as well, will be produced. In other words, there is an optimum relationship between the amounts of calcium salts and phosphates in the organism. Furthermore, other factors enter since it has been found that even under improperly balanced calcium or phosphorous diets rickets can be prevented or cured by taking cod liver oil; by exposure to sunlight; or by taking irradiated and thus activated sterols. One of these sterols derived from ergot or yeasts, when exposed to ultraviolet light becomes very potent. It can easily replace a large quantity of cod liver oil in its effectiveness. It is known as ergosterol and it is probably identical with "vitamin D."<sup>15, 16, 17</sup>

The importance of the calcium salts to the body must be evident when we consider the vital functions with which they are concerned. Calcium is essential to the maintenance of the cell membrane equilibrium; it is necessary for the contractility of the heart muscle; it must be present in the nerve-muscle excitation and irritability; it takes part in the coagulation of the blood; and it furnishes the rigidity to the skeleton. Under these circumstances it is not strange that



calcium is stored and protected, becoming available as there is a call for it.

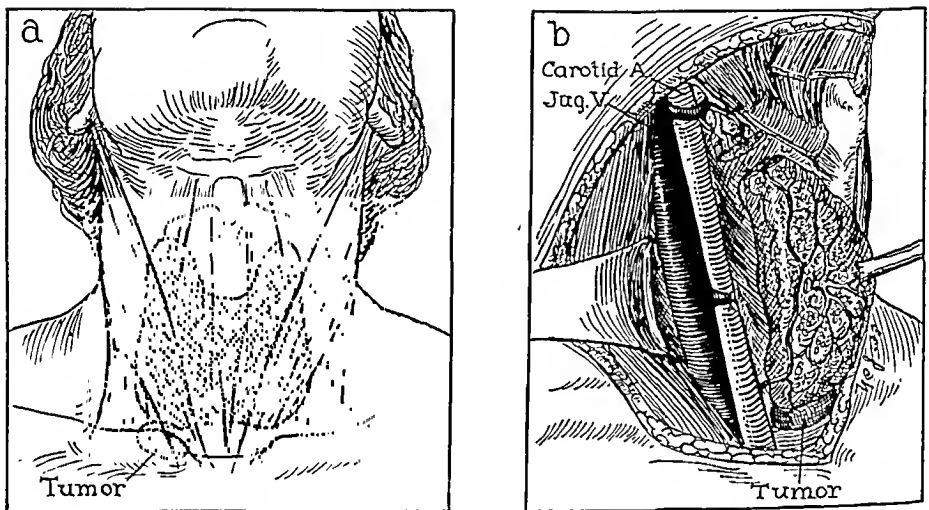
The metabolism of the calcium salts is gradually being uncovered. The diet first of all must contain adequate amounts of calcium in a soluble form. Milk and cheese furnish the best sources for calcium. Absorption takes place through the small intestine and it is conditioned by the reaction of the contents. In an alkaline medium insoluble calcium carbonate and calcium phosphate are formed. An acid medium produces more soluble acid salts. Other substances in the bowel which may interfere with calcium absorption are an excess of fats, the combination with calcium giving insoluble soaps. Also, some vegetables contain oxalic acid which combines with calcium to form insoluble calcium oxalate. Vitamin D,—as cod liver oil or activated ergosterol,—seems to increase the absorption of calcium although its exact action is still undecided. It would seem that the essential elements for a proper absorption of calcium from the intestine are a sufficient amount of available calcium, a proper degree of acidity, and some vitamin D. It goes without saying that there must be no upset in the normal digestive functions. Deficient absorption of calcium occurs regularly in some long standing fatty diarrheas, in achlorhydria from any cause, and in some allergic states. Tomato juice and orange juice which contain quantities of vitamins A, B, and C may be used in the diet to advantage although their direct relation to calcium metabolism is as yet uncertain. When once calcium has been absorbed into the blood it exists there in at least three fractions—an acid soluble fraction; an alkaline fraction bound with protein; and a biological fraction dependent especially upon the parathyroid hormone but perhaps influenced also by other internal secretions.<sup>18</sup> There is an ebb and flow of calcium from the blood to the bones and vice versa which results from the interplay of several factors. To get deposit of calcium in the skeleton there must be a proper amount of phosphate salts present,—calcium being deposited for the most part as a phosphate; the reaction in the bone must be exactly right, too much acid increasing the solubility of the calcium and decalcifying the bone; and there must be present some factor which determines the fixation of the calcium and phosphate. This is believed to be an enzyme in the actively growing centers of bone. Robison<sup>19</sup> has demonstrated such an enzyme, a phosphatase, which seems to fulfill the requirements.

FIG. 8.



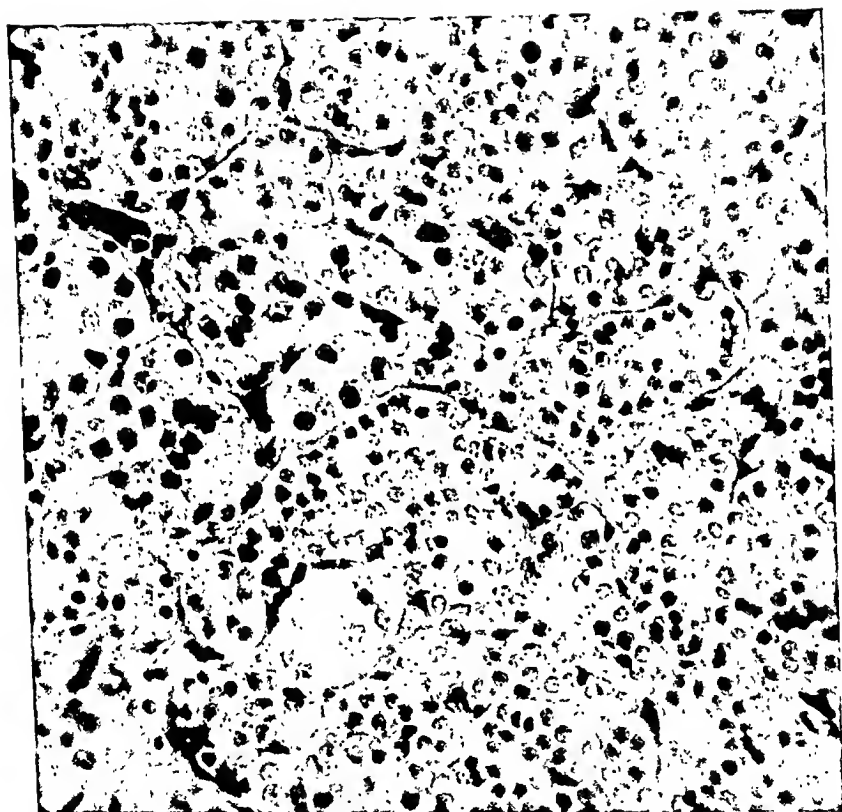
Cyst in upper end right fibula. Cyst in lower end right tibia. Two cystic areas in lower end left tibia. In the later picture these latter two cystic areas seem to be almost filled in and there is definite calcification in the cyst of the right tibia as well. This was before operation—on high calcium diet.

FIG. 9.



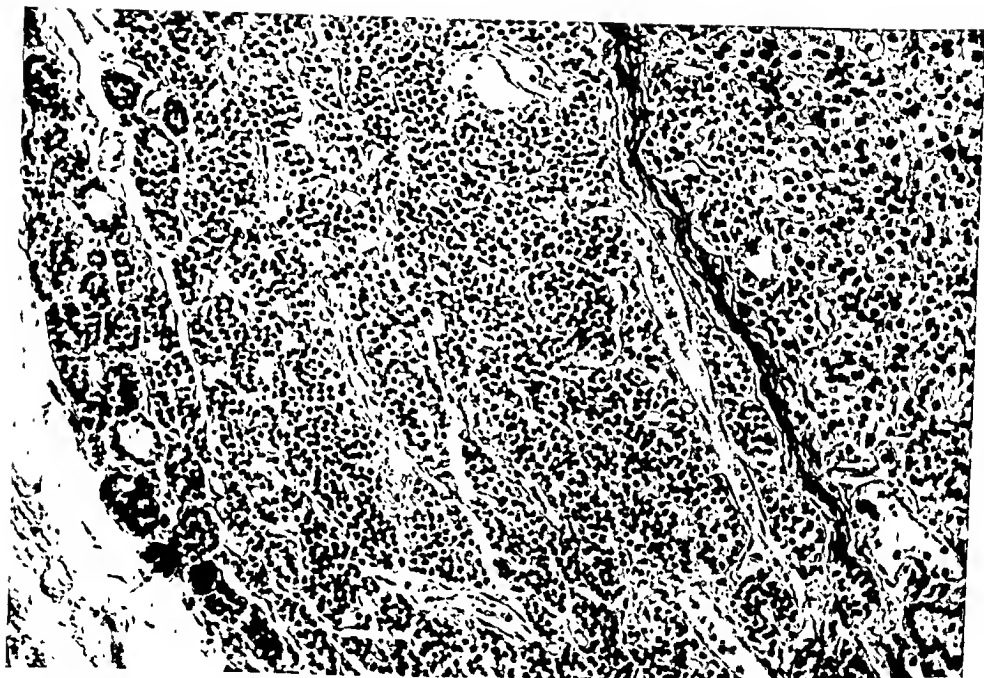
Schematic drawing showing the position occupied by the parathyroid tumor.

FIG. 10.



Photomicrograph of main portion of parathyroid tumor X 430. The pale cells are arranged in acini in regular order. Occasional larger cells with hydropic degeneration can be made out.

FIG. 11.



Photomicrograph about the edge of the tumor X 240. The main portion of the tumor is to the right. There seems to be a capsule of some sort separating a thin slice of tissue which contains at its periphery a rim of very dark staining cells in nests. Some of these contain colloid. This may represent a portion derived from a different embryological pouch. It does not seem to be thyroid tissue.

Calcium is excreted in two ways,—in the feces as calcium soaps and in combination with bile salts; and through the kidneys. There is an increased output through these channels whenever the level of calcium in the serum is much above the normal. It is possible in some pathological states to get a negative calcium balance. The importance of calcium to the functions of the body is an assurance that adequate provision for a reserve supply has been made. These calcium reservoirs have been found by Aub<sup>20</sup> to be the bony trabeculae close to the epiphyseal line. This was demonstrated by removal of limbs in animals on a high calcium diet; and later removal of the remaining limbs when the animals had been kept on a calcium poor diet. The number of bone trabeculae in the latter were markedly reduced. It was also beautifully brought out by feeding alizarin, the madder stained new bone being deposited in the trabeculae almost exclusively when calcium was being stored. Some later work has shown that the shaft to a lesser extent takes part of this function of calcium storage.

Much of our evidence on calcium metabolism comes from a study of lead poisoning.<sup>21</sup> It has been found that heavy metals like lead and radium are deposited in the bones much the same as calcium. The difference in solubility of the various metal salts constitutes a striking difference in their behavior. For example, the tertiary lead phosphate salts are relatively insoluble. The whole aim in the treatment of acute lead poisoning is to cause the circulating lead salts to be deposited in the bones as apparently harmless inert salts. This is done by giving a high calcium diet during this period. When the acute symptoms have subsided, the lead salts can be eliminated slowly by a low calcium, acid diet. The acid—phosphoric, or ammonium chloride,—transforms the trilead salt into a soluble bilead salt which is mobilized in the blood and excreted. A certain proportion of lead in the bones cannot be mobilized but remains inert under ordinary conditions. Poisoning by radium and mesothorium in dial workers is treated in the same way. Parathormone has also been used to help eliminate calcium and the other heavy metals. In the treatment of radium poisoning electroscopic tests of the stools showed a definite increased elimination of radioactive substances under this therapy.<sup>22</sup>

The clinical picture caused by an excess of parathyroid secretion is characterized by:<sup>23, 24</sup>

1. Progressive weakness and loss of muscular tonus.
2. Frequently, pain and bone tenderness in the extremities or spine.
3. Occasionally, symptoms referable to the urinary system—polyuria, renal colic from the formation of renal stones.
4. Gastro-intestinal symptoms—epigastric pain, anorexia, nausea.
5. The formation of rarefied areas in several bones,—cystic degeneration, demonstrated by roentgen rays.
6. Late cases show softening of the skeleton and progressive crippling deformities, leading to a bedfast existence.
7. Laboratory studies show:
  - a. An elevation of serum calcium above the normal—normal 10 mg., this condition 12-24 mg.
  - b. A lowering of the normal plasma phosphorus—normal 3 mg., this condition 1.5-2.8 mg.
  - c. An increased excretion of calcium, especially in the urine—this condition up to 8 times normal.
  - d. Invariably high phosphatase in the blood.

The evidence for the existence of the clinical entity of hyperparathyroidism rests on three bases:—

1. The finding of parathyroid tumors at postmortem examination in cases of multiple fibrocystic disease.
2. The removal of parathyroid tumors at operation with improvement in the clinical picture, healing of the cysts, and return to normal in the blood chemistry.
3. The production of the disease picture experimentally in animals by repeated doses of parathormone.

The prognosis is for a progression of the disease unless the cause is removed.

The treatment consists in finding the abnormal parathyroid tissue and removing it. A regular collar incision should be made as for a thyroid operation. The lateral veins should then be divided and the lateral lobes of the thyroid gland turned over toward the midline exposing the inferior thyroid arteries. The branches of these arteries should then be traced in order to identify the parathyroid glands. All four normal positions should first be explored. If no tumor is

present, the thyroid gland itself may contain what is thought to be a thyroid adenoma. Or the tumor of the parathyroid may be in the superior mediastinum or behind the trachea. A search behind the prevertebral fascia posterior to the esophagus has been necessary in some cases. Sometimes more than one tumor is present. Occasionally no tumor has been located. Some operators remove the normal parathyroids in such a dilemma.

Postoperative care consists in treating tetany if it occurs. This can best be controlled by a high calcium, high vitamin diet. Intravenous calcium therapy and parathormone may be necessary in severe cases. Ultraviolet radiation may be of assistance.

The results of treatment have been relief of symptoms, restoration of normal blood relations; and checking of the extension of the disease. In some cases no repair has taken place over a long period but in time when the damage is not too extensive, repair and healing of the cysts is to be expected.<sup>25</sup>

The pathological picture varies considerably but the usual appearance is that of large pale oxyphil cells arranged in acini. Dark oxyphil cells are occasionally seen as well. The presence of colloid is sometimes noted. Authorities differ as to whether it is a hyperplasia or a true tumor,—an adenoma.

The changes in the bone consist in a replacement of bony trabeculae by a fibrous marrow. There are small cystic spaces and in some cases collections of giant cell osteoclasts,—benign giant cell tumor. These cells are scavengers and are often filled with red blood cells or blood pigment.

The parathyroids have been believed to be responsible for certain other conditions such as focal osteitis fibrosa, Pagets' disease of bone, osteomalacia, ankylosing polyarthritis, etc.<sup>26</sup> As yet there is little evidence to warrant this assumption.

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# THE DIAGNOSIS AND TREATMENT OF PARATHYROID UNDERFUNCTION\*

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## HISTORICAL INTRODUCTION

LONG before the existence of the parathyroid glands was suspected, a remarkable symptom complex named tetany had repeatedly attracted the attention of clinical observers. Associated, as tetany often is, with dentition and lactation, with the growth of the skeleton and with the bearing of children, it is more than probable that its occurrence antedates by a considerable interval even our earliest clinical records. All cases of tetany are not of parathyroid origin, since many result from chemical changes in the body similar to, though not identical with, those resulting from disturbed parathyroid function. However, tetany is such a characteristic clinical manifestation of hypoparathyroidism, that a brief outline of its history offers the easiest approach to an understanding of parathyroid deficiency.

We shall pass unnoticed the suggestive but unconvincing allusions to tetany found in the Hippocratic and other early medical writings and begin our account with the first clear modern description published by John Clarke in 1815.<sup>1</sup> In his book on the *Diseases of Children* there is a chapter entitled, *A Peculiar Species of Convulsion in Infant Children*. "There is one variety of convulsive affection," writes Clarke, "which is more apt to be overlooked than any other, because the symptoms are not at first violent. This affection occurs by paroxysms, with longer or shorter intervals between them." He continues the description, noting the accompanying laryngeal spasm, the occasional occurrence of opisthotonos, and the precipitation of attacks by exercise. Of particular interest are the following remarks: "Accompanying these symptoms, a bending of the toes downwards, clenching of the fists and insertion of the thumbs into the palm of the hands, and bending the fingers upon them, is sometimes found not only during the paroxysm, but at other times."

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Clarke adds that in children the position of the thumb in the palm should always be viewed with concern since it may be the forerunner of convulsions.

During the three-quarters of a century following Clarke's description, medical literature is filled with recorded instances of tetany. These are, for the most part, only accurate clinical descriptions of the disorder although some contain shrewd comments upon the circumstances under which tetany occurs. We will mention only a few of the most important of these contributions.

Steinheim<sup>2</sup> in 1830 described a clear instance of idiopathic tetany, which was perhaps idiopathic hypoparathyroidism, as an unusual form of rheumatism. In the following year Dance,<sup>3</sup> writing of an intermittent form of "tetanus," remarked upon the spontaneous recovery. In 1835 Constant<sup>4</sup> emphasized the occurrence of the seizures in the first four years of life and their frequent association in later years with dentition, puberty and diarrhea. Mareska in 1845<sup>5</sup> reported an epidemic of twenty-five cases occurring in a prison at Ghent and in the next year Vleming<sup>6</sup> observed a similar epidemic in Belgium. Later (1876) another epidemic of twenty-four cases at a girl's school at Gentilly was discussed by Buzzard.<sup>7</sup> In 1852, Corvisart,<sup>8</sup> whose precise mind was offended by the variety of terms applied to one condition, suggested the term tetany, and this has since replaced the more elaborate expressions previously used to designate the syndrome. Tetany has long been known to be endemic in certain parts of Germany and Austria. There it occurred particularly during the winter months and seemed to affect especially shoemakers, carpenters and tailors.

In the reports from the medical clinic of the Hotel Dieu de Paris for 1865, Trousseau devoted a section to the discussion of tetany.<sup>9</sup> This constitutes, from a clinical point of view, one of the classics upon the subject. As early as 1846, Trousseau had noted the remarkable frequency with which lactating women were affected, and at first was inclined to regard tetany as peculiar to lactation. He soon found, however, that it often came on at the beginning of menstruation, and also during the period of growth, and later he discovered it in men. He observed tetany also during the first years of life, and particularly often at the time of dentition. In adults he found the incidence was highest between the ages of seventeen and thirty.

During the cholera epidemic of 1854, Trousseau discovered many more cases of tetany, and noting that the symptoms often developed after excessive purgation, he emphasized diarrhea as a factor precipitating the malady. He pointed out the appearance of tetany after febrile illness, particularly typhoid. He described the valuable sign now called by his name (*vide infra*), and gave an excellent description of the carpal spasm describing it as the "*main de l'accoucheur*." After noting in detail the position of the thumb and fingers, he says "*la main — affecte alors la forme d'un cone, on, si vous voulez, celle que prend la main de l'accoucheur lorsqu'il veut l'introduire dans le vagin*." Trousseau noted the prodromal sensation of formication which often precedes the attack of cramps. He divided tetany into three types; benign, in which only certain muscle groups were affected; intermediate, in which the affection was more generalized; and severe, in which the attacks were repeated and prolonged.

Erb<sup>10</sup> next advanced our knowledge of tetany when in 1874 during the course of long and detailed studies upon the reaction of motor and sensory nerves to electrical stimuli he found that far weaker currents are able to elicit responses in patients with tetany than in normal persons. Having discovered by using galvanic shocks that muscles respond to a different intensity of current when the anode is placed over the nerve than when the cathode is so placed and also that the response varies with the making and the breaking of contact, he applied these tests to patients with tetany and found that the reactions were often the reverse of those obtained in healthy persons.

Three more papers which added important details to the clinical manifestations of tetany should be mentioned. Chvostek<sup>11</sup> in 1876, reported the sign known by his name. Gowers<sup>12</sup> in 1883 described the first case in conjunction with lead poisoning. He also reported three instances occurring during the expulsion of tapeworms. Thomas<sup>13</sup> in 1895 described cases of tetany during pregnancy.

During the last decade of the nineteenth century the descriptive period of our knowledge of tetany may be said to have ended and investigation of the disorder then turned to a new direction. Although reference is said to have been made as early as 1855 by Remak, and again in 1863 by Virchow, to small structures behind the thyroid gland, the parathyroid glands were first discovered and

accurately described in 1880 by a Swede, Sandström<sup>14</sup> and at about the same time independently by an Englishman, E. C. Baber.<sup>15</sup> However, this discovery attracted no particular notice until Gley<sup>16, 17</sup> in 1891 rediscovered the glands. Like his predecessors, Gley mistakenly thought that there were only two and not four parathyroid bodies. At his operations the removal of the glands fortunately was more complete than he intended and Gley was able to show that after their removal animals died. Many of these animals developed tetany. However, in spite of these demonstrations he continued to believe that the glands were merely embryonic rests and accessory thyroid bodies.

Kohn in 1895<sup>18</sup> demonstrated that there are four parathyroid bodies. He did not consider them to be embryonic vestiges. In 1896, Vasali and Generali<sup>19</sup> showed quite definitely that removal of the parathyroid glands resulted in tetany. However, they, as well as many later investigators were led away from the true implication of these results by the assumption that the chief function of the parathyroid glands is some vague detoxifying action.<sup>20, 21, 22</sup>

As far back as 1834-5, Raynard had remarked upon the violent death of animals deprived of all thyroid tissue and in 1883, Nathan Weiss<sup>23</sup> in Billroth's clinic made what seems to have been the first note of tetany in human subjects following thyroidectomy. He found that the symptoms began from a few hours to several months after operation, a point later stressed by Rienhoff.<sup>25</sup> In 1906 Erdheim who had long been interested in the histology of the parathyroid glands, described the effects of removal of these structures.<sup>24</sup> The anatomical relations of the parathyroid bodies were most clearly established in 1906 by the work of MacCallum.<sup>26</sup> In 1905 Quest<sup>27</sup> found that the calcium content of the brain and other tissues was low in animals dying of tetany, and suggested that calcium depletion was the cause of tetany. An important advance in our knowledge was made in 1908-9, when MacCallum and Voegtlin<sup>28, 29</sup> discovered that removal of the parathyroid glands resulting in tetany was followed by a decrease in blood calcium often to one-half the normal value, and that saline and various other injections, particularly the injection of calcium salts, would relieve the tetany. Oral administration of calcium salts was effective, though slower in action. Magnesium also had some effect, but much less than calcium.

Finally Collip<sup>30</sup> in 1925 succeeded in preparing an extract of the parathyroid glands, the injection of which relieves tetany and reverses some of the chemical changes which follow removal of the parathyroid bodies.

#### ETIOLOGY

Cases of hypoparathyroidism may be divided into three groups. The first of these and the largest since the practice of thyroid surgery began, comprises those cases in which the parathyroid glands have been removed, have been injured, or have had their blood supply impaired during operation upon the thyroid gland. The second group is that called idiopathic hypoparathyroidism, in which no disease of the thyroid or other structures is apparent. Although no cause may be ascribed, yet the parathyroid glands are insufficient. A third group consists of miscellaneous cases, in which some disease of the thyroid gland seems to involve the parathyroids as well. This group is made to accommodate such cases as thyroiditis, associated with tetany, described by V. Eiselberg<sup>32</sup> and the endemic cases of tetany in conjunction with degenerative goitre found by McCarrison<sup>33</sup> in the Gilgit valley of the Himalaya mountains.

#### DIAGNOSIS

1. *Clinical Features.*—The clinical manifestations of hypoparathyroidism depend upon two basic physiological disturbances; first, hyperexcitability of the neuromuscular systems, and second, trophic changes in the hair, nails and particularly the eyes. The change in sensitivity of the neuromuscular apparatus gives rise to the symptom complex, tetany.

#### DEFINITION OF TETANY

Tetany is a condition of hyperexcitability of the central and autonomic neuromuscular systems, leading to more or less painful tonic and clonic spasms of the muscles, particularly the muscles of the extremities, but often including the muscles of the face, larynx, stomach, diaphragm and bladder, and sometimes associated with paresthesias and fibrillary twitchings. During an attack the hands and feet assume characteristic positions. The wrists are flexed, the distal phalanges extended, the proximal phalanges flexed, the

fingers adducted, the thumb strongly adducted. The position assumed led Trousseau to use the happy expression "*Main de l'accoucheur*" or obstetrician's hand in describing it. The feet and toes are flexed, the feet held intermediate between the positions called *talipes equinus* and *talipes varus*. The spasms may be confined to upper or to lower extremities or both may be involved. Although the position of the hands described above is usual and characteristic, attacks may occur in which the fingers are spread widely apart or the fist may be tightly clenched. Depending upon the severity of the attack, the face may be rigid and mask-like or distorted by the pain in the extremities. The abdomen may be rigid, the diaphragm contracted. In severe attacks, the laryngeal muscles may be involved and marked stridor occur. Often the face becomes livid and cyanotic, and the patient may die of suffocation. Laryngeal spasm is always to be regarded with grave apprehension. A slight degree of *opisthotonos* may be seen.

The smooth muscles may be involved. Spasm of the bladder has been described. The visceral as well as skeletal contractions may give rise to severe pain.

In contrast to the state spoken of as active tetany there is another state in which attacks may be precipitated by various exciting factors and during the absence of attacks hyperexcitability of the neuromuscular system may be demonstrated. This is called latent tetany. To disclose latent tetany a number of important clinical signs are sought.

*Chvostek's sign*.—Chvostek pointed out that during latent tetany, stimulation over the *pes anserinus* causes an abnormal contraction of the facial muscles. He divided the reactions into three types:

1. Percussion over the zygoma causes a faint twitching of the eye or corner of the mouth.
2. Tapping gently over the zygoma causes a marked contraction of the facial muscles on that side.
3. Slight stroking over the *pes anserinus* produces a spasm of the innervated muscles.

The second type occurs frequently; the third occurs rarely, only in very severe cases of tetany; the first occurs very often, it may be found even in normal individuals.

*Trousseau's sign*.—In 1865 Trousseau<sup>9</sup> in his lectures not only

described the characteristic position of the hand in tetany but pointed out also that during the latent stage pressure over the nerve or artery going to the affected part will bring out this characteristic spasm. To elicit Trousseau's sign we may press firmly over the nerve or artery of an extremity or we may encircle the limb, usually the arm, with a blood pressure cuff and produce pressure by inflating the bag. The pressure is maintained for five or six minutes. After from a few seconds to several minutes, depending upon the degree of hyperexcitability, the characteristic spasm appears. If there is no contraction within from five to six minutes Trousseau's sign is said to be negative.

*Erb's phenomenon.*—This is of very great value in the diagnosis of latent tetany. Erb<sup>10</sup> described the general motor hyperexcitability present in tetany and suggested a method by which this hyperexcitability could be measured. For this purpose he measured the strength of the galvanic stimulus necessary to produce a muscular response. Erb's test is strictly quantitative only in the hands of experienced observers working with accurate and unfortunately expensive apparatus. However, under these conditions the test is the most accurate of all clinical methods for detecting latent tetany and estimating its severity. The occurrence of a cathodal opening contraction with a current of less than five milliamperes definitely indicates tetany.

*Schlesinger's sign.*—Flexion of the thigh with the leg extended produces painful spasm of the leg muscles. This sign was described by Schlesinger and is often present in patients with tetany.

*Pool's sign.*—The production of spasm of the hand by forcible abduction of the arm was described by Pool in latent tetany.

*Hoffman's phenomenon.*—This consists of demonstrating increased excitability to electrical stimulation in the sensory nerves. The ulna nerve is usually employed.

*Tongue sign.*—Tapping the tongue with a sharp instrument produces dimpling due to localized contraction of the muscles of the tongue.

*Effect of hyperventilation.*—In a certain number of cases of latent tetany, in which the degree of neuromuscular hyperexcitability is below the level at which clinical signs, such as that of Trousseau, appear, these signs may be elicited after the patient has drawn a



number of very deep breaths. The increased excitability caused by hyperventilation is an important clinical aid when the diagnosis of tetany is suspected but the usual signs cannot be demonstrated.

#### TROPHIC CHANGES

In addition to tetany, changes of a trophic nature are found in hypoparathyroidism, apparently due to factors other than those which cause tetany. Of these trophic changes cataracts are the most frequent and most serious. They occur chiefly of two types. In the young they are usually nuclear, in the adult perinuclear or cortical. Degeneration of the cuboidal epithelium of the lens has been reported. In spite of much experimental work undertaken to explain the pathogenesis of these cataracts their origin still remains a mystery.

The hair may fall out, the nails become brittle and loosened in their beds.

The bones of patients suffering from hypoparathyroidism are found to be normal when examined with the roentgen ray.

#### DIFFERENTIAL DIAGNOSIS OF TETANY

Not only is tetany the outstanding symptom-complex of parathyroid underfunction, but it is the syndrome which, in most cases, discloses the malady. Occasionally in latent tetany, the occurrence of a cataract in a young individual may first arouse suspicion. When active tetany appears, or when latent tetany is demonstrated, the remaining problem in diagnosis is to recognize the kind of tetany that is present. Tetany may be classified in a variety of ways but for the purpose of differential diagnosis it is convenient to distinguish the following groups:

- 1) Tetany of hypoparathyroidism.
  - a) Postoperative.
  - b) In conjunction with thyroid disease.
  - c) Idiopathic.
- 2) Infantile tetany often associated with rickets, dentition, etc.
- 3) Tetany due to deficient calcium intake or absorption, e.g., viosterol deficiency.
- 4) Tetany due to excessive loss of calcium, usually through the bowel,—as in diarrhea, cholera, tapeworm expulsion,—but sometimes through other channels as in menstruation.

- 5) Tetany in acute febrile illness.
- 6) Tetany due to an abnormal need for calcium as occurs in pregnancy and lactation.
- 7) Tetany due to a decrease in activity of the calcium present in the blood and tissues.
  - a) Gastric tetany, (following excessive vomiting or acute dilatation of the stomach).
  - b) The tetany of hyperpnea.
  - c) Tetany following alkali injection.
  - d) Tetany following alkaline phosphate injection.

Occasionally tetany may be dependent upon more than one factor. Diarrhea, for example, may complicate hypoparathyroidism; or, as is often the case, a defective calcium intake may be combined with some abnormal demand for calcium such as occurs for instance during pregnancy. Therefore, tetany is often attributed to the wrong factor or to only one of several factors concerned.

The history of the patients' illness is often of considerable value in aiding us to ascertain the form of tetany. For instance, if the thyroid gland has been removed a few hours or even several months before, we at once suspect parathyroid deficiency. Usually, however, it is only by chemical examination of the blood that an accurate diagnosis of the type of tetany may be made. Thus, if the total serum calcium is normal (9-11 mg. per 100 cc. of serum), the parathyroid glands, in all probability, are not deficient. Again if the serum calcium is normal and the blood chlorides are low, a condition usually due to vomiting or to the accumulation of a large amount of fluid in a greatly dilated stomach (Dragstedt),<sup>34</sup> "gastric" tetany is indicated. Yet again if the blood calcium is normal and the carbon dioxide combining power of the plasma is high we suspect alkalosis, due perhaps to hyperpnea or to alkali ingestion, to be the cause of the tetany.

In distinguishing infantile tetany, the age of the patient, the frequent association with rickets or with diarrhea are perhaps of more assistance than the blood chemical findings. In infantile tetany the serum inorganic phosphorus is often elevated, the serum calcium somewhat lowered.

Tetany of parathyroid origin is practically always marked by a low serum calcium (below 8.5 mg. per 100 cc.) and an elevated serum

inorganic phosphorus (above 4.5 mg. per 100 cc.). A low total serum calcium is often found in conditions which lower the serum proteins,\* or after prolonged diarrhea (in adults as well as children), or when the calcium intake is grossly inadequate. During pregnancy and lactation the unusual demand for calcium if coupled with a grossly inadequate intake first depletes the maternal bone reserve of calcium and later may result in lowering of the calcium of the blood. With the exception of *parathyroid deficiency*, in all of the many conditions in which the serum calcium may be low, the serum inorganic phosphate is usually *not* elevated and may also be low. This point, in addition to the history, gives the clue to the diagnosis. There is one condition in which the blood calcium and phosphate values might be mistaken for those of hypoparathyroidism. This is chronic nephritis with renal insufficiency. Here there is found a high serum phosphate and this together with the lowered serum protein content often results in a very much lowered total and also active serum calcium. That tetany is not more frequent in these cases is largely due to the acidosis which is usually present. The recognition of nephritis at this stage is not difficult and seldom causes confusion with parathyroid deficiency. The calcium and phosphorus changes in nephritis have recently been discussed in detail by Peters.<sup>35</sup>

#### CHEMICAL CONSIDERATIONS IN HYPOPARATHYROIDISM

The work of MacCallum and Voegtlin was largely responsible for focusing attention upon the calcium metabolism in parathyroid deficiency. Greenwald,<sup>36, 37</sup> another pioneer in the study of the physiology of the parathyroid glands, soon thereafter indicated the importance of changes of phosphorus as well as of calcium metabolism in parathyroid underfunction. Since the introduction of the parathyroid extract of Collip, a number of papers<sup>31, 38, 39, 40, 41, 42</sup> have appeared describing the action of this hormone and the various metabolic abnormalities which result when it is absent or present in in-

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\* The author wishes to avoid here any discussion of such questions as ionized and unionized, diffusible and non-diffusible calcium, etc. It should be recognized, however, that that portion of the calcium combined with protein is physiologically inactive. The reduction of total calcium due to decrease of serum proteins does not, therefore, affect the active serum calcium.

sufficient amounts. For detailed information the reader may consult these papers.

The most important and well known chemical change which follows removal of the parathyroid glands and the one which we must still hold to be directly responsible for the production of tetany is lowering of the *active* serum (and perhaps tissue) calcium. However, the active serum calcium may also be lowered under certain circumstances when the parathyroid glands remain intact and when it is sufficiently lowered, no matter by what means, tetany will result.

In the presence of parathyroid deficiency anything which tends to lower further the active serum calcium, will increase the severity of the tetanic manifestations. The two principal factors which decrease the active serum calcium are:

- 1) factors which decrease the total calcium and with it the active fraction, such as grossly deficient intake of calcium, viosterol deficiency, excessive loss of calcium from the body as in diarrhea, lactation, pregnancy, etc.
- 2) factors which decrease the activity of the calcium in the blood, such as alkalosis (overbreathing, excessive vomiting, alkali injection), or retention of phosphates in the blood (which often causes reduction of the total calcium also).

In 1901 J. Loeb<sup>45</sup> produced muscular twitchings by injecting salts that would precipitate calcium. Binger<sup>46</sup> in 1917 found that the injection of phosphoric acid or sodium phosphate caused a lowering of blood calcium and that injection of alkaline phosphates resulted in tetany.

The active serum calcium is increased by the ingestion or the injection of large amounts of calcium, by the administration of viosterol,<sup>53</sup> by conditions which decrease the serum phosphate, by the injection of acid<sup>47</sup> or other conditions producing acidosis.

From metabolic studies the principal changes which follow removal of the parathyroid glands may be summarized as follows:<sup>41</sup>

1. Decrease in phosphorus excretion in the urine.
2. Rise in serum inorganic phosphate.
3. Fall in serum calcium.
4. Decrease in calcium excretion in the urine.
5. Increase in neuromuscular excitability.
6. Tetany.

Administration of parathyroid extract corrects the foregoing as follows:<sup>41</sup>

1. Increase in phosphorus and, to some extent, of water excretion in the urine.
2. Fall in serum inorganic phosphate.
3. Rise in serum calcium.
4. Increase in calcium excretion in the urine.
5. Relief of tetany.

The calcium and phosphate content of the stools is not markedly affected by the parathyroid hormone.<sup>38</sup>

It is interesting to compare the metabolic alterations of parathyroid hyperfunction with those of parathyroid hypofunction. The former are exactly comparable to the effects of injection of parathyroid extract.

- 1) Increased phosphorus excretion in the urine.
- 2) Fall of serum inorganic phosphate.
- 3) Rise in serum calcium.
- 4) Increase in calcium excretion in the urine.
- 5) Marked loss of calcium and phosphate from the body with resultant bone changes.

#### COURSE OF THE DISEASE

The particular course of a given case of hypoparathyroidism depends upon how much active parathyroid tissue is present, the extent of the demands made upon that tissue and the type of treatment. In the untreated case the disease is often characterized by exacerbations and remissions, particularly if it is a mild case. Sometimes attacks of tetany are precipitated by some obvious factor, such as exercise or diarrhea, at other times no cause for the exacerbation may be apparent.

#### TREATMENT

In a recent paper<sup>44</sup> the author has discussed the rationale of the present treatment of hypoparathyroidism. Therapeutic measures are adopted in order to achieve two purposes. The first of these is to relieve the tetanic crises and to prevent the occurrence of the occasionally fatal laryngeal spasm. The second is to effect, if possible, a permanent cure of the parathyroid deficiency. In many cases, under the stimulus of parathyroid underfunction, the remaining parathyroid tissue hypertrophies and eventually becomes quite ade-

quate to meet the needs of the body or at least nearly so. In his experiments upon parathyroid grafts, Halsted (1909)<sup>43</sup> emphasized that no graft was successful unless a parathyroid deficiency existed, and that excessive parathyroid tissue would not live. Moreover, those who have removed a hyperfunctioning parathyroid adenoma are very familiar with the acute deficiency which often rapidly follows the operation. The treatment outlined here, is devised to relieve the patient of symptoms, by utilizing the chemical knowledge of the disorder acquired by elaborate metabolism experiments, without doing away at once with all parathyroid deficiency. It is hoped by this means to encourage the patient's good or remaining parathyroid tissue to adequate activity.

*Low Phosphorus Intake.*—The restriction of the phosphorus intake is based upon the following two important considerations. First, during hypoparathyroidism the elimination of phosphate in the urine is low and the serum inorganic phosphate is high. That this interferes with the activity of the calcium present and also decreases the amount of calcium in the serum is highly probable (*vide supra*).<sup>40</sup> Second, it has been shown that when the ratio of phosphorus to calcium in the diet is low the absorption of calcium is facilitated.<sup>55</sup> Shelling<sup>48</sup> has shown that in rats a low phosphorus intake is definitely beneficial and Albright and Ellsworth<sup>39</sup> and Ellsworth<sup>44</sup> have used a restricted phosphorus intake for some time in treating human beings. It is possible to restrict the daily intake of phosphorus to 1.0 Gm., or slightly less, by proper selection of foods. However, such a diet lacks variety and soon becomes distasteful so that patients are often persuaded with difficulty to take it for a long time. The use of the low phosphorus diet has been discussed in a recent paper.<sup>44</sup> The foodstuffs constituting a low phosphorus diet are found in Appendix A.

*High Calcium Intake.*—This has been used ever since the experiments of MacCallum and Voegtlin.<sup>29</sup> Hunter and Aub<sup>50</sup> found that parathyroid extract was more effective when used in conjunction with a high calcium intake. This would be true whether the hormone was of endogenous origin or was given by injection. The high calcium intake is obtained by using foods high in calcium content and by adding calcium salts to the food. The lactate (14 per cent. Ca) and the gluconate (10 per cent. Ca) are now often used. The carbonate (40 per cent. Ca) is also employed. 2.5 to 3.0 Gm. or

more Ca daily is a fairly high intake and this amount may be successfully given by adding to the diet the calcium salts described above. In the mildest cases of parathyroid deficiency with slight tetany, the use of a high calcium and low phosphorus diet alone may relieve the condition.

*Calcium Chloride.*—This deserves especial mention and is considered apart from other calcium salts because it acts in two ways to combat the faulty metabolism of parathyroid deficiency. It does so (1), by reason of its high calcium content (36 per cent.) and (2) because it tends to produce a slight acidosis, which in itself is beneficial (*vide supra*). By making a 45 per cent. solution, very large amounts of calcium may readily be administered (4.0 or more Gm. daily). It is a most important remedy since even very severe cases, as a rule, respond to its use.

*Thyroid Extract.*—This has not yet been much used in the treatment of hypoparathyroidism, but since in postoperative cases some thyroid deficiency often occurs, it is of considerable interest to know that thyroid extract has a favorable effect upon the symptoms of parathyroid deficiency. Aub, Bauer, Heath and Ropes<sup>51</sup> studied the effects of the thyroid hormone upon calcium and phosphorus metabolism. Although in hyperthyroidism the serum calcium and phosphorus levels were found to be normal, there was an increased urinary excretion of both calcium and phosphorus. Similarly the administration of thyroid to a normal individual, though affecting the serum levels only slightly, or none at all, brought about an increase in the excretion of calcium and phosphorus in the urine. With regard to the use of this hormone in cases of hypoparathyroidism, where the serum calcium and urine calcium excretion are low, the serum phosphorus high and the urine phosphorus low, Aub, Albright, Bauer and Rossmeis<sup>52</sup> have recently reported interesting results. They found that following thyroid administration the serum calcium rose. Only after it had reached a normal level did the calcium excretion increase appreciably. The urine phosphorus excretion, however, was increased immediately and very definitely. This effect was observed soon after the thyroid administration was begun. The level of the serum phosphorus was very little affected. This work indicates that thyroid administration by increasing phosphate excretion and raising the level of calcium in the blood may be very useful in the treatment of hypoparathyroidism.

*Irradiated Ergosterol.*—This substance has recently been highly recommended for controlling the tetany of hypoparathyroidism.<sup>54</sup> There are many conflicting ideas about its action owing partly to difference of dosage and partly to the failure to control other factors, such as the calcium and phosphorus intake. In one of our cases,<sup>43</sup> the use of viosterol was followed by untoward effects. The serum calcium at first rose and then returned to its former level. The serum inorganic phosphorus was increased and active tetany came on.

On the other hand, in the recent careful observations of Bauer, Marble, and Claflin<sup>53</sup> upon a patient with hypoparathyroidism, the administration of irradiated ergosterol in combination with large amounts of calcium chloride and a moderately restricted phosphorus intake resulted in a marked rise of serum calcium and fall of serum inorganic phosphorus. That this effect was due at least in part to the calcium chloride was shown by the fact that when the calcium chloride was reduced and the ergosterol continued, the reverse effect took place, i.e., the serum calcium fell and the inorganic phosphorus rose.

Shelling<sup>49</sup> has reported that large doses of viosterol will raise the blood calcium and alleviate the symptoms of tetany in parathyropivic rats.

Certainly in one of our cases the effects of viosterol were unfavorable. It is possible that the dosage (4.0 cc. daily, viosterol 250D) was too large, or that it is necessary to use a very high calcium intake with this vitamin to obtain good results.

*Parathormone.\**—The desirability of allowing some degree of parathyroid deficiency to remain has already been emphasized. For this reason parathyroid extract should be regarded as an emergency measure, as the last, even though a most potent, resource. The effect of the extract upon calcium and phosphorus metabolism has already been discussed. Loss of effectiveness when used over a long period of time has been observed. This is an additional reason for employing the extract only as an emergency therapeutic aid, rather than as a full substitute for the endogenous hormone.

*Summary of Treatment.*—We may outline the treatment of a case of parathyroid underfunction somewhat as follows. The patient, if not having laryngeal spasms, is put to bed at rest. The diet is

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\* Isolated by Collip and prepared by Eli Lilly and Company.



arranged so that it shall contain less than 1.0 Gm. daily of phosphorus and more than 2.5 Gm. daily of calcium (by the addition of calcium salts). If this does not result in relief, the calcium intake may be increased to 4.0 Gm. or more daily. If the symptoms still persist, calcium chloride (45 per cent. solution) may be administered, 4 to 12 cc. three times a day. Relief even in severe cases usually follows. Thyroid extract one-half grain twice daily may be used as an adjunct. Viosterol in small doses may also be tried. If the calcium chloride does not effect relief, parathormone 1 cc. (20 units) is given, up to five times a day if necessary, to obtain the desired effect. As a rule, when parathormone is necessary, a single injection of 1 to 2 cc. daily for three to five days is usually sufficient to abolish the tetany. The regime outlined above may then be instituted.

If, on the other hand, the patient is suffering from laryngeal spasm, it is usually prudent to institute active measures at once. Ten cc. of 10 per cent. calcium chloride diluted to 200 cc. with normal saline (0.9 per cent.) may be given intravenously followed by 10 cc. of 45 per cent. calcium chloride by mouth. It is sometimes necessary to repeat this three to six hours later. In addition, 1-2 cc. of parathormone intramuscularly may be given. The dietary regimen is then started and calcium chloride and parathormone are used as described above only when an emergency recurs.

## APPENDIX A

*Eat no foods except those listed*

- Breakfast: 1 serving fruit  
 1 strip crisp bacon  
 1 small slice toast with butter and jam or honey
- Luncheon: 1 small serving potatoes  
 2 servings vegetables  
 1 serving fruit or gelatine with fruit  
 1 small slice bread and butter
- Dinner: 1 oz. chicken  
 1 serving vegetables  
 lettuce salad  
 1 small slice of bread  
 1 serving fruit or small custard

### FRUITS

Apples (1)  
 Bananas (1)  
 Cranberries  
 Grapefruit ( $\frac{1}{2}$ )  
 Grapejuice ( $\frac{1}{2}$  glass)  
 Lemon

### VEGETABLES

Asparagus  
 Beets  
 Cabbage  
 Carrots  
 Celery  
 Cucumbers

Cantaloup ( $\frac{1}{2}$ )

Orange (1)

Orange juice ( $\frac{1}{2}$  glass)

Pears (1)

Peaches (1)

Strawberries

Watermelon

Lettuce

Winter or summer squash

Tomatoes

Turnips

Radishes

These may be added to diet in fairly large amounts

Butter and salad oil

Honey

Jam and jellies

Sugar

Gelatine

Egg white

Shrimp—either canned or fresh

Salt and pepper

Tea and coffee

Cream (only in small amounts)

In place of 1 oz. of chicken (cooked) you may use:

1 oz. halibut or haddock

3 oz. oysters

1 oz. crab flakes

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## TETANY OF THE NEWBORN.

Clinic by DR. HARRIET G. GUILD, The Harriet Lane Home, Johns Hopkins Hospital, November 7, 1932.

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THIS is a discussion of tetany in the newborn, a rare condition and one that is extremely difficult to diagnose. The discussion is precipitated by a case seen in the Obstetrical Department in the fall and brought to the Harriet Lane Home a few hours before death. The admission note summarizes the situation so well that it is quoted here.

Baby Girl H., H. L. 79333. Note on admission by Dr. Washington.

This two day old infant caused alarm immediately after birth by failure to breathe properly. Respirations were extremely rapid and shallow and accompanying cyanosis caused an oxygen tube to be arranged immediately. Other findings at this time were a rather depressed fontanelle, prominent precordium with more distinct cardiac dulness than normal and a musical systolic murmur at the left sternal border, and slight spasticity of all extremities. The impression was that intraeranian hemorrhage had occurred.

On the following morning respirations were much improved. However, there was then nystagmus, slight internal strabismus, increased spasticity and more marked "jitters" than normal. The baby took breast milk, 20 cc. every 4 hours, well. She cried normally.

This morning the picture has changed. Some spasticity, internal strabismus, nystagmus, and "jitters" remained, but in addition there occurred, especially when disturbed, spastic seizures during which the back arched, all muscles stood out, and respirations ceased. This lasted less than thirty seconds. The tonus gradually relaxed and respirations recommenced, accompanied at first by marked laryngeal stridor which gradually subsided. Also, there was moderate permanent cyanosis, and the chest had a remarkable fullness anteriorly making the antero-posterior diameter enormous. Heart and lungs seemed perfectly normal. Chvostek and peroneal reflexes were positive. A slight amount of old blood was vomited. The diagnosis now was uncertain. Hemorrhagic disease with perhaps intraeranian hemorrhage from this cause was suggested. On the other hand, the seizures suggested tetany and it should have been mentioned that these attacks were followed often by violent normal crying as though from discomfort. After a sedative she was given blood into her buttocks and also calcium gluconate. A lumbar puncture was then done which brought clear spinal fluid. A calcium determination on this was 3.9 mg. per cent. A diagnosis of tetany of the newborn was made.

During the day cyanosis persisted in spite of continuous nasal oxygen, the "emphysematous" appearance of the chest remained. She refused to swallow anything and vomited more "coffee-ground" material, the seizures became less

frequent, although the general condition declined. Mucous or aspirated vomitus rattled in the trachea at times. Calcium was again given intramuscularly.

Tonight because of failure to improve the baby was transferred to the Harriet Lane Home.

The points in the record regarded as suggestive of tetany were the combination of convulsions and tonic spasms with positive Chvostek and peroneal signs, a laryngeal stridor that suggested laryngospasm, and a slightly low calcium concentration in the spinal fluid. At first the baby seemed relatively normal between convulsions, but later some difficulty in swallowing developed, and in spite of calcium therapy the general condition became worse and death ensued. Since blood could not be obtained from the baby for calcium determination, the mother's blood was examined in the hope that it might yield some information of value. Her blood calcium was 9 mg. per cent.

I shall take up these points one at a time and illustrate the difficulty in evaluating the signs of tetany in the newborn.

(1) *Convulsions*.—Unless carpopedal spasm is present (for that is always suggestive of tetany) there is nothing about the convulsions of tetany that is characteristic enough to differentiate them from convulsions due to other causes. The tonic nature of the spasms is stressed here, but such spasms are very common in intracranial hemorrhage and are more often confused with tetanus than with tetany. The fact that at first the baby seemed relatively normal between convulsions justifiably suggested tetany, but this state did not continue and the development of additional symptoms such as difficulty in swallowing, pointed rather away from tetany and more toward intracranial hemorrhage.

(2) *Chvostek and peroneal signs*.—A positive Chvostek is an almost constant finding in newborn infants, so that in itself it cannot be regarded as a sign of tetany during the neonatal period. In infants showing a positive Chvostek, the peroneal sign is also present when it is possible to make a satisfactory test.

(3) *Laryngeal stridor*.—This has also been described in the course of intracranial hemorrhage. Three cases of intracranial hemorrhage, confirmed at autopsy, are reported in which laryngospasm was an outstanding symptom.<sup>1</sup> It was so marked in one that

<sup>1</sup> MUNRO, D.: "Three cases of Laryngeal Spasm Associated with Intracranial Hemorrhage in the Newborn," *Ann.Otol.Rhinol.& Laryngol.*, 34:677-681, 1925-1926.

tracheotomy was performed. In none was any abnormality of the larynx found at autopsy and the laryngospasm was believed to have been due to a disturbance in the respiratory center, resulting from the hemorrhage.

(4) *Spinal fluid calcium*.—The average normal spinal fluid calcium, which corresponds to the diffusible calcium in the blood, is 5 mg. per cent. In other words, it averages from 45 to 50 per cent. of the total blood calcium. The limits of normal, as indicated by a collection of all figures given in the literature, are from 4 to 6 mg. per cent. In this case it was 3.9 mg. per cent., only .1 mg. below the figures given for the lower limit of normal.

What correlation can be drawn between the spinal fluid and blood calcium? Parallel determinations made on the blood and spinal fluid in conditions in which the blood calcium is disturbed (including tetany) have failed to show any constant variation in the spinal fluid. Occasionally there has been a slight decrease in the spinal fluid calcium when there was a marked decrease in the blood but more often, even with marked changes in the blood, the spinal fluid calcium has remained normal. In one or two instances it appeared to go down a little as the blood calcium went up, or vice versa. The fact that the spinal fluid calcium was rather low in this case, though suggestive, cannot be regarded as satisfactory evidence of tetany. It is only slightly below the lower limit of normal and if it did parallel the blood calcium and represent 45 per cent. of that (the average lower limit in terms of ratio between the two) it would indicate a blood calcium of nearly 9 mg. per cent. (8.9 to be exact). No positive conclusions can, therefore, be drawn from the spinal fluid calcium in this case.

(5) Can any conclusions be drawn from the level of the mother's blood calcium? Parallel determinations of the blood calcium in mother and child immediately or shortly after delivery invariably show that under normal conditions, the mother's calcium is lower than the child's. The difference varies from 0.5 to 2 mg. per cent. and the lower the mother's calcium, the greater is the discrepancy between mother and child. Statistical reports in the literature and the few figures we have obtained on the Obstetrical Service here all agree on this point. Since the mother's calcium in this case was 9 mg. per cent., it is of value only in suggesting a normal calcium

level in the baby's blood, and, therefore, gives no clue as to the possible presence of tetany arising from any cause within the baby itself.

An analysis of all the points in this history that suggested tetany fails, therefore, to yield satisfactory evidence that tetany was present. The most we can say is that we cannot prove its absence, especially since the spinal fluid calcium was somewhat low, though I do not believe that the baby had tetany. The symptoms and course were so much like that of intraeranian hemorrhage, that from a clinical standpoint I should regard that as the more probable diagnosis, even in the face of a lumbar puncture that yielded fluid free from blood. The later vomiting of coffee-ground material suggests that the infant had hemorrhagic disease. It is possible that a small hemorrhage into the substance of the brain that failed to reach the subarachnoid space at first may have increased in severity as the hemorrhagic tendency appeared so that it would have been apparent had a second lumbar puncture been done. Further manifestations of hemorrhagic disease may have been prevented by the intramuscular injection of blood.

Although an autopsy was done, even that was not wholly satisfactory in clearing up the questions raised by the clinical course of this baby. The autopsy was not performed until several days after death, and at that time the brain was so soft that it could not be examined in detail. A hemorrhage was found in the substance of the left occipital lobe, but the examiner could not determine whether or not it communicated with the ventricle, and the brain was not saved. The parathyroids also were not saved, so we do not have access to the two tissues of most value here. Dr. Park found no indication of rickets in the bones that were delivered to him.

A review of cases of tetany reported in the literature is also rather unsatisfactory because of the incompleteness of the evidence produced in favor of the diagnosis. Too much stress is usually put upon the positive Chvostek and peroneal signs, and calcium determinations—if made at all—have usually not been made until after calcium therapy had been given. Dr. Weech told of several authentic cases seen in China, in which the mothers were the subjects of tetany during pregnancy. Such cases are quite understandable as are the cases of "congenital rickets" in babies of mothers with



osteomalacia. Other cases reported in infants who have vomited incessantly during the first few days can be explained on the basis of gastric tetany, but neither of these is in point here.

I have had access to the records of three other babies in whom the diagnosis of tetany was made or suspected.

(1) Dr. Powers in New Haven referred me to this case. The patient was a full-term baby, normal delivery, breast fed with some supplementary feeding in addition, who showed slight stiffening attacks at six days of age, some right-sided twitching at seven days, and finally generalized convulsions at eight days. A blood calcium determination showed a value of 7.5 mg. per cent. Calcium chloride was given and the convulsions stopped though slight twitching was observed during the next twenty-four hours. Calcium therapy was continued for two weeks, though the baby's progress was uneventful after the first day of treatment. The low blood calcium and prompt response to calcium therapy seem to warrant the diagnosis of tetany here.

(2) Dr. Caulfield's patient in Hartford. This was a large full-term baby whose delivery was sufficiently difficult to produce a fracture of the clavicle. Convulsions started on the eighth day. They became more frequent in spite of treatment with all kinds of sedatives. Lumbar puncture on the eleventh day yielded fluid that contained red blood cells and a trace of globulin (no note as to xanthochromia of the supernatant fluid). At fourteen days the position of the hands suggested tetany and the Chvostek (not previously tested) was found to be positive. Calcium therapy was started, but avertin by rectum was given simultaneously. The convulsions ceased the next day, after the baby had been under the influence of avertin all night. No blood calcium determination was made, and the evidence at hand points more toward intracranial hemorrhage than toward tetany. Even the therapeutic test was complicated by the use of avertin.

(3) This was an infant in the Harriet Lane Home last winter, admitted at the age of ten days with a history of severe diarrhea since two or three days after birth. Twitching movements of face and arms, noted at the time of admission, were said to have been present for several days, and the baby was thought to have been unusually "jittery" ever since birth. The Chvostek was actively

positive. His blood showed a low calcium (6 mg. per cent.) and a high phosphorus (9.5 mg. per cent.), suggesting a parathyroid tetany. The spinal fluid was also faintly xanthochromic, later becoming markedly so. An overdose of parathormone (given because of failure of response of symptoms to calcium) resulted in a blood calcium of 20 and phosphorus of 15 mg. per cent. at the time of death. Autopsy revealed a large intracranial hemorrhage, and normal parathyroids. The absence of other hemorrhagic phenomena—especially intestinal hemorrhages—makes it impossible to attribute the intracranial hemorrhage to the overdose of parathormone. Furthermore some evidence of hemorrhage was present before any medication was given. I think we can feel certain that this baby had tetany, but we cannot correlate his *symptoms* with the tetany since there was also intracranial hemorrhage, and the symptoms never responded to the therapy given for the tetany.

From all the facts presented, we may conclude that tetany occasionally occurs in the newborn—perhaps as a result of some transient functional disturbance in the parathyroid glands—but that it is almost impossible to make a diagnosis on clinical evidence alone. All of the symptoms and signs are so closely simulated by other conditions belonging to the neonatal period that laboratory confirmation, in the form of a low blood calcium, is essential to the diagnosis.

#### DISCUSSION

*Dr. Edwards A. Park:* Will you tell us how frequently the Chvostek is positive in the newborn and for how long? Is it conceivable that it might be increased in cases of intracranial hemorrhage?

*Dr. Guild:* The Chvostek is positive in at least 85 per cent. of all newborns and usually persists for at least two weeks. Dr. Dunham of New Haven says that in a small percentage of babies the Chvostek persists for as long as two months. It is a typical Chvostek and varies from just a flicker around the eye to an extremely active response involving the eye, nose and lip. It is conceivable that it might be increased in cases of intracranial hemorrhage but it would be valueless unless one knew how active it was before the onset of the condition.

*Dr. Park:* Convulsions of tetany in the offspring of women with tetany in China is entirely understandable, just as the presence of rickets in the offspring of women with osteomalacia is perfectly understandable and I should think there was every reason to suppose that tetany might occur similarly. I was under the impression that obstetricians did not recognize early forms of osteomalacia. In New Haven Dr. Dunham discovered very marked rickets in a child one month old. The question arose as to whether the mother had had osteomalacia. The mother returned and I think it was apparent that the mother had osteomalacia but it had not been striking enough to arouse the suspicions of the obstetricians. It is a question as to whether tetany and osteomalacia can escape the notice of the obstetricians.

You have demanded, Dr. Guild, that we be far more circumspect in making the diagnosis of tetany in the newborn than we have been in the past. You call attention to the fact that evidence is negative and it seems to me that it would be fair to ask what evidence we ought to present. You point out that the Chvostek and peroneal phenomena do not count in the newborn child and that carpopedal spasm may occur in a child with defective development of the central nervous system and intracranial hemorrhage. You rather force us to base the diagnosis on the chemical determinations in the blood. You demand that the chemical determinations of the blood must be those of tetany and that there must be no other conditions to account for the symptoms. What symptoms justify a suspicion of tetany and what procedures ought we to adopt in making the diagnosis?

*Dr. Guild:* (1) Convulsions without other adequate explanation should arouse a suspicion of tetany, especially if there is any suggestion of carpopedal spasm and if the baby seems normal between convulsions. A response of symptoms to calcium therapy is also suggestive evidence of tetany. Unusually pronounced "jitters" may arouse suspicion, but this is often so marked in perfectly normal babies during the first few days that it cannot be emphasized very strongly. Certainly the Chvostek and peroneal signs are of no value. (2) Calcium determinations on the blood offer the only positive evidence of tetany.

*Dr. Park:* I think a parathyroid relationship with tetany might be established. An attempt has been made to explain tetany on the

grounds of hemorrhages into the parathyroids. I have read an article in the *Zeitschrift* stating that it is a fact that on autopsies in children dying a short time after birth one does find hemorrhages in the parathyroids. I noticed them myself again and again at the New York Foundling Hospital. I think there has been a complete failure to correlate this with any symptoms of tetany. The possibility of a functional disturbance of the parathyroids remains, since so many mechanisms of the newborn do not work right during the first two or three weeks of life and then later adjustments take place. In that case the premature baby might be expected to show signs more often than the full-term baby. Dr. Guild's cases were in full-term babies. The child observed in the Harriet Lane Home with tetany was said to have been three weeks premature, but weighed seven pounds at birth so probably was really a full-term baby.

# Medicine

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## THYREOHYPOPHYSEAL SYNDROME OF LONG DURATION; ADULT MYXOEDEMA IN ASSOCIATION WITH HYPOPHYSEAL NEOPLASM

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IN MAKING diagnostic studies of endocrinopathic cases, conservative internists try, as far as possible, to attribute the symptoms in any given patient to a single glandular disturbance rather than to multiglandular involvement. For a time, the diagnosis of "polyglandular endocrinopathy" was all too popular and was often a cloak either of actual ignorance of the implications of uniglandular maladies or of negligence in making the studies sufficiently complete.

Undoubtedly, however, syndromes are met with that can be explained only upon the basis of disturbed function of two or more glands, or even of a majority of the endocrine glands as in Falta's "multiglandular sclerosis." In the patient here to be described we have, I think, indubitable evidence of marked disturbance of function of at least two important glands, namely, the thyroid and the hypophysis cerebri. An attempt has been made, however, to make clear the possibility that the hypothyroidism may have been due to deficient production of the thyreotropic hormone of the anterior lobe of the hypophysis.

### CASE HISTORY

William T., fifty-two years of age, a retired farmer (now a furnace man), was admitted to Ward Osler 6 (service of Professor Longcope), on January 24, 1933, for study.

**CHIEF COMPLAINTS.**—Increasing dimness of vision, increasing deafness for many years, and marked increase in weight.

**FAMILY HISTORY.**—Members have shown tendency to obesity. One brother suddenly lost sight in right eye when about fifty; another brother lost sight in right eye following an illness. Father and one brother died of "dropsy." Mother died of "asthma."

**PAST HISTORY.**—Aside from ordinary diseases of childhood, two minor motor accidents, hemorrhoids, and a temporary facial palsy that followed

exposure, there seem to have been no symptoms of illnesses except those that pertain to his existing malady.

He was a farmer until two years ago when he retired and since then has taken but little exercise. He has always been a liberal eater, and occasionally has had digestive upsets after dietary indiscretions. Many teeth have been extracted because of caries and toothache. He has been obese for many years; his weight has increased, especially since leaving the farm, and he has often felt shortness of breath upon exertion.

He was at school until his sixteenth year, reaching the seventh grade before leaving to go to work. He married and became the father of eight children, five of whom are living and well. His wife was killed in a motor accident some six years ago.

**PRESENT ILLNESS.**—It is difficult to determine the date of onset of the illness that has given rise to his present state. A photograph of him at the age of twenty reveals no striking abnormality in appearance. Though his calculated ideal weight for his height is about 110, he states that at twenty-five he weighed 150 pounds, and, at forty, 180 pounds; during the past two years there has been a rapid increase of weight to 218 pounds. Between the ages of thirty and thirty-five, he noticed that he walked more slowly, accomplished less than before, and was very sensitive to cold (though he perspired when hot). When about thirty-five, he noticed that he could not hear so well; the deafness progressed during the following ten years to such a degree that he could not understand conversation unless spoken to in a loud voice. He noticed, too, that, rather suddenly, somewhere between his thirty-fifth and fortieth year, the hairs of his beard, armpits, and mons pubis began to fall out and, in time, practically disappeared; there was also some falling of the hair of the head, especially in front but much of this grew in again later. His skin became dry and cracked easily. For the past ten years he has often felt drowsy in the daytime but has not slept well at night. His memory has failed gradually in recent years, especially during the past two years. He states that he has always drunk much water and passed much urine, though he rises only once at night to urinate. During the past two years he has been markedly constipated, having bowel movements only three times a week. Libido and potentia were normal up to the time of his wife's death six years ago. His vision has grown gradually but steadily worse; he has had, he asserts, especial difficulty in seeing things on either side of him, whereas things directly in front of him are better seen.

**PHYSICAL EXAMINATION** (Drs. Clark, Winkenwerder, and King).—A summary of the positive findings on admission, made by the clinical clerk, Mr. Warren Sears, includes:—Height 5 feet, 1 inch; weight 218 pounds (about 100 pounds above calculated ideal weight); temperature 99.6° with, however, somewhat subnormal temperature since admission; pulse rate 70, later, after rest, 56 to 68; respiratory rate 20; blood pressure systolic, 140 mm. Hg, diastolic, 90 mm. Hg at first, later 126/80 mm. Hg.

Skin thick, dry, wrinkled and fissured, especially over distal parts of extremities. A few pedunculated moles. Fingers and toes short and thick; no lunulae of nails visible. Pads of fat in lateral parts of upper eyelids; puffiness below the eyes; large accumulations of fat in the breasts, abdomen and buttocks. Hair of head delicate, dry and brittle; almost devoid of beard, hair and crines pubis.

Slight cyanosis of lips; very large tongue; many missing teeth; pyorrhoea alveolaris; tonsils rather large and scarred. Thyroid not definitely felt. Short thick neck.

Heart's apex not visible or palpable; area of cardiac dulness enlarged, especially to the left; heart sounds distant; soft systolic murmur at apex.

Right testis smaller than left, but no genital dystrophy. Tender, non-bleeding hemorrhoids.

Hypoactive knee-jerks.

**LABORATORY TESTS.**—*Blood*: Jan. 24th, red count 4,010,000; Hbg. 87%; white count 4,840; no marked change in differential count (31% lymphocytes); platelets normal; fasting blood sugar 86 mgm. %; blood calcium, 11.2 mgm. %; phosphorus 4.1 mgm. %; cholesterol 208 mgm. %. Wassermann reaction, negative.

Jan. 29th, red count 3,630,000; Hbg. 78%; white count 4,000; bleeding time 3 minutes.

*Urine*: Specific gravity 1.018-1.022; negative for albumin, sugar and casts.

*Mosenthal Test*: Specific gravity of total urine between 7 P.M. and 6 A.M. 1.010. Then 500 cc. water given. Specific gravity at 8 A.M. 1.018; at 10 A.M. 1.016; at 12 noon 1.018. Then 500 cc. of water given. Specific gravity at 1 P.M. 1.013; at 2 P.M. 1.013; at 4 P.M. 1.022.

*Glucose Tolerance Test*: 125 Gm. glucose (dissolved) by mouth at 9 A.M. (fasting blood sugar 85 mgm. %).

After	½ hour	—135	mgm. %
"	1	"	—155
"	2	"	—130
"	3	"	—105

*Insulin Tolerance Test*: Fasting sugar 85 mgm. %; 2 units of insulin given intravenously; blood sugar after 15 minutes 84; after ½ hour 77; after 1 hour 81; after 2 hours 85.

*Adrenalin Test*:

Before administration.....B.P. 125/85; bl. sugar 85 mgm. %

5 min.	after 1 cc. injected intramuscularly	B.P.	150/85		
10	"	"	"	"	150/90
15	"	"	"	"	150/90
30	"	"	"	"	130/85
45	"	"	"	"	125/85
1 hour	"	"	"	"	120/90
2	"	"	"	"	118/75
					130
					174
					198
					150

*Basal Metabolic Rate*: Minus 22 (Jan. 25th); minus 27 (Jan. 30th); tests satisfactory.

*Roentgen ray Examinations* (Dr. Ostro): *Skull plate* shows markedly enlarged sella turcica, with destruction of posterior clinoids.

*Teleroentgenogram measurements*: M. R. 5.2; M. L. 10.5; A. 5.8; L. 16; total width of chest 32. Heart moderately enlarged.

*Chest plate*: Thickened pleura over right apex; trachea pulled to the right; suggestion of mass in upper mediastinum, possibly a substernal thyroid (Dr. C. A. Waters).

*Hands:* Epiphyseal junctions all united; some lipping of edges of bones at junction with cartilages (hypertrophic osteopathy).

*SPECIAL EXAMINATIONS.—Electrocardiographic Report* (Dr. Bedell): Rate 68; sino-auricular rhythm; P-R interval varies from 1.24 to 2 seconds or longer; duration of Q R S .07; T-I inverted; R-II slurred and notched.

*Report on Nose, Throat and Ears* (Dr. Dill): Ear drums intact, slightly retracted; hears all forks by AC in both ears except that C 2048 and C 4096 are not heard in either ear. AC greater than BC in both ears. No fixation of stapes (Lewis test). Weber not referred. With Bárány alarm hears spoken voice well. Nose, nasopharynx, larynx and paranasal sinuses negative.

*Impression:* (1) No focus of infection in ears, nose or throat; (2) bilateral nerve deafness.

*Psychiatric Report* (Dr. W. Muncie): Mental status practically normal considering his education; has managed a farm of 140 acres satisfactorily; answers to questions are a little slow but, on the whole, adequate; no anergastic features.

*Ophthalmological Report* (Dr. Walsh): The dry thick folds of skin are remarkable. Lids thickened; slight reddening of conjunctivae of upper lids. Corneae clear. Pupils react normally to light; only the left pupil reacts on accommodation. Aside from weakness of convergence, extraocular movements are normal. Tension normal.

R.E.V. no gl.—sees hand movement at one foot.

L.E.V. no gl.—20/100; clearer with pin hole.

On ophthalmoscopic examination: R.E.—lenticular opacity at periphery. No vitreous opacities. Margins of disc somewhat indistinct. Marked optic atrophy. L.E.—essentially same as R.E.

Charts of visual fields show for the left eye loss of sight in temporal half, for the right eye quadrant defect in lower nasal field; slight concentric contraction of fields in both eyes. Lesion probably in upper part of right optic tract causing incomplete left hemianopsia; in addition, some bilateral optic nerve atrophy.

*Medical Neurological Report* (Dr. F. R. Ford): Negative findings except for visual disturbances referable to the right optic tract, probably due to pituitary tumor.

*Surgical Neurological Report* (Dr. Walter Dandy): Pituitary tumor; poor operative risk at present.

#### DISCUSSION OF THE MAIN FEATURES OF THE CASE

Through a consideration of some of the principal findings in this patient we can most easily arrive at justifiable conclusions regarding the pathological physiology and the pathogenesis of the malady.

*The Visual Disturbances.*—Nearly twenty years ago, the patient's vision became impaired and, despite the wearing of glasses, there has been progressive deterioration of visual acuity since. Objectively, in addition to his error of refraction, his presbyopia, and his faulty convergence (possibly dependent upon his poor vision), he has



slight concentric restriction of the visual fields, and a left homonymous hemianopsia (complete in left eye, lower quadrantic in right eye) and on ophthalmoscopic examination there is definite evidence of bilateral pallor of the optic discs. These data point to diffuse lesions of both optic nerves and a lesion of the right tractus opticus.

*The Auditory Disturbances.*—About seventeen years ago, he noticed that he was becoming deaf. Since then the deafness has grown gradually worse, so that he can understand only loud conversation. There is bilateral impairment of auditory acuity. The tests made with tuning forks indicate loss of tone perception for higher tones (fork C 2048 and C 4096) in both ears, whereas lower tones are well heard, a finding that points to bilateral nerve deafness (cochleae, cochlear nerves or the cochlear paths as they pass cerebralward). Again he hears better by air-conduction than by bone conduction ("positive Rinne test"), which adds further support to the view that we are not dealing with "middle-ear deafness" but with "nerve deafness."

*The Mental State.*—Aside from the patient's statement that between the ages of thirty and thirty-five he found that he could not accomplish as much as formerly, that he became sluggish in his movements, and drowsy in the daytime, the only other mental symptom complained of is impairment of memory in recent years, and especially in the past two years. On careful tests by Dr. Muncie of the Phipps Psychiatric Clinic the mental status, considering the patient's education, did not seem to be abnormal, except perhaps for some slowness of response to questions asked; there is certainly no evidence of psychotic or of psychoneurotic anomalies.

*The Circulatory System.*—There has been, after rest, a rather marked bradycardia (pulse rate 56 to 68) and slight cyanosis of the lips. The apex beat of the heart was not visible or palpable (but the patient is markedly obese). The heart is enlarged (percussion; teleröntgenogram) to both the right and the left and a soft systolic murmur has been audible at the apex. There is no arterial hypertension. Definite anomalies are apparent in the electrocardiogram; the P-R interval is prolonged to 1.24 sec.; the duration of Q R S is .07 sec.; T-I is inverted; and R-II is slurred and notched.

Attempts to record simultaneously phlebograms and arteriograms were unsatisfactory as the skin of the neck is very thick and rough.

That there is dilatation of both sides of the heart is evident and there is evidently beginning disturbance in the atrioventricular conduction system.

*The Blood.*—There is a secondary anemia (with high color index and some anisocytosis and poikilocytosis, but no marked macrocytosis) and a leucopenia, but there are no marked changes in the differential count of the white cells. The fasting blood sugar averages 86 mgm. %. It would be very interesting to determine the blood iodine content by von Fellenberg's method, but this has not yet been done; the test is valuable since with it one can estimate the blood iodine content in millionths of a gram (gammas or  $\gamma$ ) in 100 cc. In normal blood, the iodine level is found to vary between 7.5 and 12.5  $\gamma$  %, in the blood of Basedow's disease from 15 to 90  $\gamma$  %, and in myxedema from 4 to 6  $\gamma$  % (A. Schittenhelm).

*The Digestive System.*—Owing to the patient's condition, the stomach contents have not yet been examined. He has suffered from severe constipation having bowel movements only three times a week; and there are some tender non-bleeding hemorrhoids.

*The Urogenital System.*—The patient reports slight nocturia, but he drinks much water and there has been oliguria. The urine is of rather high specific gravity (1.018-1.022), but has been otherwise negative. The patient has suffered no loss of libido or potentia, at least up to the time of the death of his wife, and he has been the father of eight children. Though the right testis is somewhat smaller than the left, there are no signs of general sexual dystrophy.

*Metabolic and Endocrine Conditions.*—The patient is of small stature, being only 5 feet, 1 inch in height. The epiphyseal junctions in the roentgen ray film of the hand are united.

The patient has always been obese; though his calculated ideal weight for his height is only 116, he weighed 150 pounds in his twenty-fifth year, 180 pounds in his fortieth year, and during the past two years has gained very rapidly so that on admission he weighed 218 pounds (at least 100 pounds above his calculated ideal weight). Though there is general excess of fat, the masses about the breasts, abdomen and buttocks are disproportionately large. Though his appetite has always been good and, of late, he has taken less exercise than formerly, the degree of obesity he shows could

scarcely be of exogenous origin entirely; it must be, in part, of endogenous (endocrinopathic) origin.

The skin is thick, dry, wrinkled and fissured over the face and in the eyelids and especially over the distal portions of the extremities. He is, however, capable of perspiring in hot weather and on exertion. The marked hypotrichosis has been a salient feature, and, particularly, the rapid loss of the hairs of the beard, of the hirci and of the crines pubis about fifteen years ago.

The basal metabolic rate has been retarded; it was found to be minus 22% on admission and minus 27% a few days later.

Roentgenograms of the lateral skull have revealed a marked enlargement of the sella turcica and some destruction of the posterior clinoid processes, findings strongly suggestive of hypophyseal neoplasm. If the injuries to the optic pathways are to be regarded as neighborhood symptoms, the growth must have been developing over a very long period (twenty years), evidence in favor of a benign form of growth, perhaps originating in the ductus cranio-pharyngeus.

#### DIAGNOSTIC CONCLUSIONS

If we now think of the case as a whole, there would seem to be sufficient reason for making the following multidimensional diagnosis:—

1. Hypophyseal neoplasm (perhaps originating in the ductus cranio-pharyngeus) with enlargement of the sella turcica, destruction of the posterior clinoid processes and pressure upon the visual conduction paths at the base of the brain, but without headaches or other phenomena pointing to general increase of intracranial pressure.
2. Hypothyroidism with myxedema [causing characteristic changes in the skin and its appendages (hairs; nails) and dilatation of the heart, retardation of the basal metabolic rate, contributing to the obesity, giving rise to marked sensitiveness to cold, to chronic severe constipation, to drowsiness and to sluggishness of movements and thoughts, and making the knee jerks hypoactive].
3. Obesity (more than 100 pounds overweight), partly of exogenous, partly of endogenous origin.

4. Myocardopathy with dilatation of the cavities of the heart and with characteristic changes in the electrocardiogram (*q.v.*).
5. Bilateral optic atrophy and incomplete left homonymous hemianopsia.
6. Bilateral nerve deafness.
7. Moderate anemia (R.B.C. 3,630,000; Hb. 78%) with leucopenia.
8. Pyorrhoea alveolaris.

COMMENT ON THE POSSIBLE RELATIONS OF THE DISEASE OF THE  
HYPOPHYSIS TO THE HYPOTHYROIDISM THROUGH CURTAILMENT  
OF MANUFACTURE OF THE THYREOTROPIC HORMONE OF THE  
ANTERIOR LOBE

The patient never grew tall, has always been obese, for twenty years or longer has had visual symptoms that we now know must have been due to the neoplasm in the hypophyseal region, and for about the same length of time has shown symptoms and signs suggestive of underactivity of the thyroid gland. Were the tendencies to dwarfism and to obesity due to disturbance of hypophyseal function, to insufficiency of thyroid function, or to both? It is difficult to be sure, for the patient may have been somewhat thyreoaplastic from birth on as well as hypophyseopathie.

The thyreopathy could not have given rise to the hypophyseopathy but could the latter have been responsible for the former? There is growing evidence in favor of the view that the anterior lobe of the hypophysis manufactures a hormone that stimulates the thyroid to activity, just as it produces sex hormones that stimulate the gonads to certain activities. Uhlenhuth and Schwartzbaeh (1927) found that atrophy of the thyroid occurred after removal of the hypophysis and that this could be overcome by injections of anterior lobe extracts or by implantation of anterior lobe. Leo Loeb (1928-9) and Kaplan and others showed that histological changes in the thyroid (not unlike those seen in hyperthyroidism) can be produced in experimental animals by injection of anterior lobe extracts. Paal and Huber (1931) isolated a substance, which they believe is a specific hormone of anterior lobe origin; when it is injected into white mice it will (like the blood serum of patients suffering from

exophthalmic goitre) protect them from poisoning by acetonitril (Reid Hunt reaction). Its protective action is, however, exerted through stimulation of the thyroid since transplantation of anterior lobe material into animals protects them from acetonitril poisoning only when their thyroids have not been removed. Paal has given to this thyreotropic anterior lobe hormone the name "hormothyrin" and thinks that it may be identical with the anterior lobe hormone ("theta" substance of Crew) that stimulates metamorphosis of Axolotl larvae (Swingle; Spaul) since the latter, too, appears to act through the thyroid as an intermediary.

In view of the presence of a tumor in the hypophyseal region in the patient here described, it is conceivable that, in the injury of the anterior lobe, the manufacture of its thyreotropic hormone may have been curtailed with resulting atrophy of the thyroid gland and hypothyroidism. If so, we would have to assume that the injury to the hypophysis has resulted in a dissociation of the activities of that gland, since the manufacture of the hormones that stimulate the gonads does not seem to have been stopped.

#### TREATMENT OF THE PATIENT

Surgical intervention for removal of the tumor at the base of the brain is quite impracticable at present because of the general condition of the patient. Dr. Read Ellsworth has been much interested in trying the effects of the thyreotropic anterior lobe hormone upon the patient; after five doses (one ampoule intramuscularly daily) the basal metabolic rate has become less retarded, a determination today giving a reading of minus 16. If there is not sufficient response to this hormone, desiccated thyroid will be given in sufficient dosage to substitute for the patient's inability to produce enough thyroxin. The cardiac condition will probably improve under this therapy though other cardiogenic measures may also be necessary. The weight will gradually be reduced by thyroid treatment and by means of the reducing diet of Evans. The anemia will probably yield to hematinic measures and to treatment of the pyorrhoea alveolaris. Before resorting to surgery for removal of the neoplasm at the base of the brain, even after the patient's general condition has been greatly improved, it might be well to make a thorough trial of deep roentgen ray therapy.

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# THYROTOXICOSIS "MASKED" BY NORMAL OR SUB-NORMAL BASAL METABOLIC RATE\*

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THE clinical picture of thyrotoxicosis as manifested in outspoken cases of Graves' Disease and in patients having nodular goiter with hyperthyroidism is familiar to all. The eye signs, particularly lagging of the upper lid on looking downward, and the stare, with or without exophthalmos, the tremor, the tachycardia, the forceful contractions of the heart resulting in loud heart sounds and, in the later stages, the frequent presence of auricular fibrillation, the high pulse pressure, the goiter, which is usually demonstrable, complete a striking clinical picture which, when fully developed, is recognized at a glance. This clinical entity we have come to associate with an increase in the basal metabolic rate.

It often happens, however, that the patient does not present such a clearly defined condition. There are all gradations between normal individuals and those with frank hyperthyroidism.

Patients suffering from hyperthyroidism without the fully developed clinical picture have been referred to in the French literature for years as "*formes frustes*" and in American literature under the designation of "masked" hyperthyroidism. Excellent papers dealing with this type of patient have been published recently by Levine<sup>1</sup> and by Hamburger and Lev.<sup>2</sup> Levine discusses particularly unrecognized hyperthyroidism masked as heart disease. In none of his patients was there exophthalmos or obvious goiter. The diagnosis was based on such data as the general appearance of the patient; warm, moist, hyperemic and slightly pigmented skin; greater comfort in cold weather than in warm; brief attacks of diarrhea or vomiting; great loss of weight; alert, quick movements; often a peculiar stare, a tremor of the fingers, and at times transient glycosuria. He looks upon transient auricular fibrillation as the most characteristic cardiac finding. The heart sounds are peculiarly loud. A suggestive finding is the failure to obtain the usual reduction in

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the heart rate with digitalis. Levine makes the further statement: "After a suspicion is aroused concerning the possibility of an unrecognized hyperthyroidism by one or more of the above criteria, a careful basal metabolic rate determination must be made. If this is within normal limits, the diagnosis can be dismissed." Co-existing organic heart disease, such as angina pectoris, hypertensive heart disease or mitral stenosis, makes the diagnosis even more difficult. The relief which followed subtotal thyroidectomy was either complete, or marked improvement was obtained.

Hamburger and Lev have also given an excellent discussion of the subject, with a review of the literature. They discuss hyperthyroidism masked by congestive heart failure, by anginal heart failure, associated with organic heart disease of rheumatic or arteriosclerotic type, or masquerading as diabetes mellitus or as pernicious vomiting. Their five illustrative cases were all associated with increase in the metabolic rate, and great benefit was obtained from subtotal thyroidectomy.

Wohl<sup>3</sup> reports seven cases, improved by operations on the thyroid. In one with a nodular goiter and normal metabolic rate, the post-operative relief of symptoms was complete.

Cases similar to those reported by Levine, Hamburger and Lev, and Wohl are not uncommon and are easily overlooked, unless examined with special reference to the possibility of thyroid disease. It is particularly important in the patients with manifest rheumatic heart disease or other forms of heart disease, to bear in mind the possibility of an added thyroid factor. Several months ago a colored man was admitted to the wards with mitral stenosis of rheumatic origin, and auricular fibrillation, with the usual symptoms and signs of congestive heart failure. Examination disclosed the presence of a goiter and other signs of thyrotoxicosis with a metabolic rate of  $+8$ . A subtotal thyroidectomy was carried out after preliminary treatment had been instituted, and a few days after operation fibrillation ceased. The rhythm has remained normal. There has been no recurrence of the symptoms of circulatory failure.

It is not so generally recognized that the clinical picture of hyperthyroidism or of masked hyperthyroidism, i.e., thyrotoxicosis, may be met with in patients with a normal or subnormal basal metabolic rate. In recent years we have been impressed with the frequency of this condition, and largely through the opportunity of work in



association with Dr. Mont R. Reid, we have seen many such patients entirely relieved of symptoms or greatly benefited by subtotal thyroidectomy,<sup>4, 5</sup> and have become more and more impressed with the worthlessness of the basal metabolic rate determinations in the management of thyrotoxicosis. This point has been emphasized by Graham<sup>6</sup> and by Reid,<sup>7</sup> both of whom have operated on many patients with evidences of thyrotoxicosis but with normal or subnormal rates.

It seems clear, therefore, that there is a fallacy in basing the clinical diagnosis and treatment on the results of the determination of the basal metabolic rate. If the rate is normal or subnormal in the presence of manifest symptoms and signs of thyrotoxicosis, the usual inference is that subtotal thyroidectomy is contraindicated. Yet, as the result of fairly extensive experience, we are convinced that this is not true and that *the metabolic rate should be entirely disregarded when there is clinical evidence of thyrotoxicosis* and a demonstrable goiter. In one of our patients, a metabolic rate of  $-32$  prior to operation had risen to  $+12$  one year after operation, with relief of the thyrotoxic symptoms without further treatment.

Thyrotoxicosis may be masked, therefore, by a normal or subnormal basal metabolic rate, and is generally amenable to the same treatment, namely, subtotal thyroidectomy, as applied to patients with increased metabolic rate. It seems probable that these states are usually the result of a pre-existing stage, in which the basal metabolic rate has been elevated. As Reid expresses it, the disease is "burned out," so far as the increased oxygen consumption is concerned. The pathological physiology in these cases is obscure, but the relief of symptoms and the frequent return of the basal metabolic rate to normal from a subnormal level indicates that disturbed function of the thyroid is at fault. Furthermore, the result of operative treatment shows that some disturbance in the thyroid causes a continuance of the thyrotoxic symptoms and signs, regardless of the basal metabolic rate.

Exactly the same operative treatment is indicated for thyrotoxicosis masked by normal or subnormal metabolic rate as in the cases with increased metabolic rate, as already stated. This applies to patients with a "thyroid heart" as well as to patients with other forms of heart disease, in whom a masked thyrotoxicosis with normal or subnormal rate is discovered. In the latter, one of the difficulties

is that, prior to operation, one cannot evaluate accurately the relative importance of the thyroid, when other etiological factors are also involved. In many cases the result obtained by operation on the thyroid gland is so striking that the clinical problem is greatly simplified. Elsewhere we have reported illustrative cases.

The foregoing remarks apply both to patients with diffuse and nodular goiters, demonstrable either on physical or roentgen ray examination. The physical examination for goiter requires very careful inspection and palpation of the neck, according to the technique described by Lahey.<sup>8</sup> With intrathoracic goiter, roentgen ray films furnish important evidence.

#### CONCLUSION

*The basal metabolic rate, while very helpful when it is elevated, is a sign which should be ignored, when normal or subnormal, in the presence of unmistakable evidence of thyrotoxic symptoms and signs. Particularly in the presence of heart disease, operative treatment is indicated, regardless of the basal metabolic rate.*

For the present we have adopted the policy of ignoring a normal or subnormal rate *only when there is a demonstrable goiter*. Without this limitation the difficulties of diagnosis might lead to unwarranted operations for neurocirculatory asthenia and other conditions which often simulate the nervous manifestations of thyrotoxicosis. Fortunately, in such cases, true heart disease is relatively rare.

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# AGRANULOCYTIC ANGINA AND ALLIED CONDITIONS

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AGRANULOCYTIC angina is an acute or subacute disease characterized by extreme leukopenia and ulcerative lesions of the oral cavity or of the mucous membranes elsewhere in the body. The majority of cases occurs in females and the disease has a strong tendency to recur, should the patient survive the first attack. In untreated cases the mortality is very high (Doane).<sup>1</sup> The condition is also referred to in the literature as agranulocytosis, granulopenia, malignant neutropenia and pernicious leukopenia.

A second condition—the malignant neutropenia of sepsis—is often most difficult to distinguish from true agranulocytic angina. Usually sepsis is accompanied by an increase of the peripheral white blood cells and a great increase in the percentage of polymorphonuclear neutrophils. In certain cases, however, the bone marrow fails to respond in the normal manner and there ensues, sooner or later, a leukopenia and an almost complete disappearance of the granular cells. It is to this state of affairs that we refer as the malignant neutropenia of sepsis.

In the present paper we are primarily concerned with the consideration of the two disorders. In each there is leukopenia, often of an extreme grade. In each the prognosis is very grave. In each the essential therapeutic aim should be to raise the level of the white cells in the blood.

The following cases illustrate, as well as may be, examples of these conditions.

CASE 1.—A married man was admitted to the Massachusetts General Hospital on December 22, 1931.\* The patient's past and family history were unimportant. Two months before entry he noticed that the toes of his left leg were red, swollen and tender. The condition grew worse and a month later he had a series of chills. Three days before admission there were again chills and the

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\* I am indebted to Dr. Francis T. Hunter for permission to report this and the following case.

patient noticed that there were ulcerations and blebs on his face and buttocks and a sharply defined gangrene of the toes of the left foot. It is important to note that at this time the blood findings were essentially normal. First the left foot was amputated and then a week later it was necessary to remove the left leg at the hip. After a stormy convalescence the patient was discharged much improved on February 6, 1932.

After a few days at home the patient became worse. There appeared an ulceration of the left buttock which exuded thin watery serum. He was readmitted to the hospital February 10, 1932. At this time his white blood cells

CHART 1.



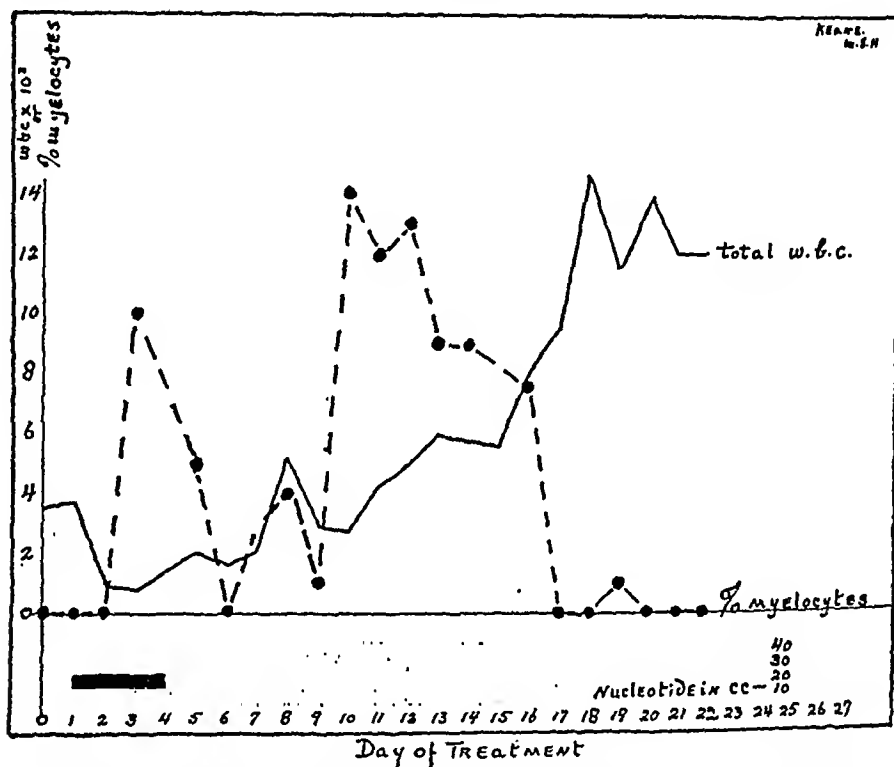
Temperature Chart on Case I.

were 4,000 per c.mm. without polymorphonuclear neutrophils. The temperature on entrance was 101° F. and it rose rapidly to 104° F. (Charts 1 and 2.) Coincidentally the white blood cell count fell to 2,000 per c.mm. The patient was semiconscious and deeply intoxicated.

In view of the comparatively low white blood cell count and the complete absence of polymorphonuclear neutrophils, treatment with pentnucleotide (N.N.R.) was immediately instituted, 10 cc. twice a day for three days. At the end of this period his clinical condition appeared better, but coincidentally his total white blood cell count had fallen to 1,100 per c.mm. (Chart 2.) The myelocytes, previously absent, had risen to 10 per cent., indicating that the bone marrow was again actively functioning. Owing to the mechanical difficulty of either intramuscular or intravenous therapeutics, the pentnucleotide was reduced to 10 cc. a day. The total white blood cell count rose to 5,200 per

c.mm. but fell rapidly again and the myelocytes virtually disappeared so that on February 26th, ten days after admission, 40 cc. pentnucleotide were given and thereafter the same amount was administered each day for six days. Following the first of the larger doses there was a sharp increase of myelocytes (Chart 2) and the white blood cell count gradually rose to 9,500 per c.mm. and it remained essentially normal thereafter. As these favorable hematological changes were taking place a coincident improvement occurred in the patient's general condition. The temperature fell to normal, the ulcerations healed, his strength returned and he was discharged well on April 2nd, seven weeks after entry.

CHART 2.



White blood cell count, percentage myelocytes and pentnucleotide treatment on Case 1.

In this case we were dealing with a leukopenia secondary to an infected gangrene in a debilitated arteriosclerotic patient. There appears to be no question but that the improvement was brought about by the pentnucleotide and, furthermore, in this instance there seemed to be a fairly close parallelism between the amount of pentnucleotide administered and the magnitude of the myelocyte response and of the subsequent increase in white blood cell count.

In the majority of cases the first indication of a favorable result from pentnucleotide therapy is a very considerable increase in the number of myelocytes. Such an increase took place in this case on the third day of treatment. A rise of total white blood cells usually follows. Such a rise in this case took place on the seventh day of treatment. Owing to the reduced treatment this rise, however, was not maintained and only after a greatly increased dosage was there a marked and sustained improvement in the peripheral blood picture.

CASE 2.—C. E. D., a married American physician, entered the Massachusetts General Hospital, May 23, 1931. In 1918 he had had pansinusitis. In early May 1931 he had caught cold and once more developed sinusitis. One week later the condition became worse and the patient developed fever and marked malaise. From that time on he became rapidly worse. Weakness was extreme. His temperature ranged between 99° and 102° F. Two days before entry both ethmoids were opened and drained but only very thin pus was obtained and no clinical improvement followed. For three days before entry the white blood cell count varied between 400 and 600 per c.mm. without any polymorphonuclear neutrophil cells. One day before admission the lids of the right eye became markedly swollen. On entrance the patient was irrational, disoriented and extremely ill. There was marked tenderness over the frontal, ethmoid and maxillary sinuses on the right. There was diffuse redness of the throat. The temperature was 103° F., the pulse 120. The red blood cell count was 3,820,000 per c.mm., the hemoglobin 10.9 Gm. per hundred cubic centimeters, the white blood cell count 800 per c.mm., polymorphonuclear neutrophils 10 per cent., lymphocytes 75 per cent., monocytes 7 per cent. and unclassified 8 per cent. Platelets were greatly increased. He was given 10 cc. pentnucleotide intravenously on May 23rd, 24th and 25th and 5 cc. intramuscularly on May 27th, 28th, 29th, 30th, 31st and June 1st and 2nd. By May 28th, five days after the initiation of pentnucleotide therapy, the white blood cell count had risen to 1,600 per c.mm. with 64 per cent. polymorphonuclear neutrophils, 32 per cent. lymphocytes and 4 per cent. monocytes. On June 1st the white blood cell count was 5,000 per c.mm. with 69 per cent. polymorphonuclear cells. Two days later the white blood cell count had risen to 7,500 per c.mm. At this time the differential count showed 57 per cent. polymorphonuclear neutrophils, 34 per cent. lymphocytes, 8 per cent. monocytes and 1 per cent. unclassified cells. The temperature gradually fell to normal on May 26th, four days after treatment was begun, and clinical improvement was marked from that day on. June 9th a radical ethmoid and antrum operation was done by Dr. Harold Tobey. The white blood cell count rose to 24,900 per c.mm. the next day but then fell to normal and remained there until the patient's discharge, cured, a month later.

These two cases are typical of the malignant neutropenia of sepsis. The condition occurs equally in the two sexes and is not uncommon in children. It may follow almost any kind of infection. We have seen it in pneumonia, sinusitis, appendicitis, empyema, osteomyelitis and solitary liver abscess. In any infection the bone marrow may fail to respond adequately to the demand for leukocytes and there ensues, gradually or rapidly, a more or less marked leukopenia. Coincidentally, younger and younger cells of the granular series make their appearance in the blood and there are found in the smear polymorphonuclear neutrophils showing toxic degeneration—namely vacuoles in the cytoplasm and large deeply staining cytoplasmic granules. The malignant neutropenia of sepsis is an

ominous sign and, as in agranulocytic angina, the essential therapeutic consideration is that of raising the white blood cell count level to normal. That the causative lesion must also be adequately treated goes without saying.

The following case is typical of the true idiopathic agranulocytic angina.

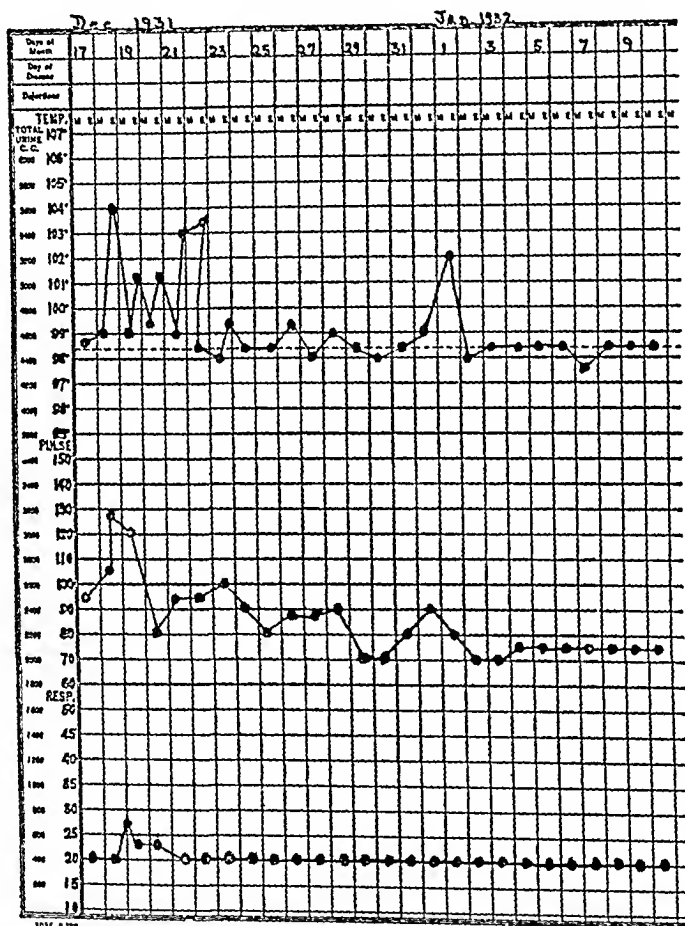
CASE 3.—(B. C. H. 657628) A widowed American woman of thirty years entered the Boston City Hospital December 17, 1931. Her past history is interesting and important. She was entirely well until February 1930 when after a few days of general malaise she had quite suddenly a series of sharp chills and a temperature of 104° F. The following day she had generalized muscle pains and ulcerations of the gums rapidly developed. No blood studies were made at this time. She was acutely ill for ten days with continuous fever and marked prostration. The temperature then fell to normal and she rather gradually regained her strength and health. No specific therapy was used.

All went well until March 16, 1930 when she noticed that her gums were again sore. The same day she had chills, marked prostration and a temperature of 104° F. Her throat was extremely painful. The white blood cell count was found to be 1,600 per c.mm. and no polymorphonuclear neutrophils were seen in the smear. For four days she continued in this condition and the blood remained essentially as on entrance, but then the temperature rather suddenly dropped to normal. At the same time the white blood cell count abruptly rose to 5,400 per c.mm. and mature polymorphonuclear neutrophils to 56 per cent. Convalescence was uneventful. Again no specific therapy was used.

In June 1930 she had another attack of sore throat and extreme prostration. At this time her white blood cells dropped to 650 per c.mm. and there was again complete absence of polymorphonuclear neutrophils. During this illness superficial ulcerative lesions appeared on the hands and buttocks and she developed a left parotitis. After a few days all symptoms and signs subsided, the white blood cell count rose to a normal level and she remained well until August 1930, when she had again ulcerative lesions in the mouth and it was found that her white blood cell count was 500 per c.mm. For two weeks her white blood cells never rose above 2,000 per c.mm. and no polymorphonuclear neutrophils appeared in the smear. Recovery this time was very gradual and only after several weeks was she symptomatically well. She then remained in good health until December 1931. From time to time blood counts were done in view of the past history. On December 15, 1931 she felt perfectly well and was about her usual duties, but her white blood cell count was found to be found to be 3,000 per c.mm. with but 20 per cent. polymorphonuclear neutrophils. The next day she continued to feel well, but the white blood cell count had fallen still further to 500 per c.mm. and the polymorphonuclear neutrophils were only 2 per cent. There was no obvious infection from a clinical point of view. The following morning her white blood cell count was 700 per c.mm., yet she still felt perfectly well. She was admitted to the hospital and was given 10 cc. pentnucleotide (N.N.R.) intramuscularly twice a day. Following each injection she was nauseated; occasionally she vomited. The next day her temperature rose to 104° F. and she continued with an irregular tem-

perature ranging from 104° F. in the evening to 99° F. in the morning. (Chart 3). On December 22nd, five days after entrance, she complained of considerable pain in the lower rectum and perineum. Careful examination showed no lesion. Except for this symptom she felt much better, although the temperature remained elevated. Her white blood cell count had risen to 1,000

CHART 3.



Temperature Chart on Case 3, December, 1931.

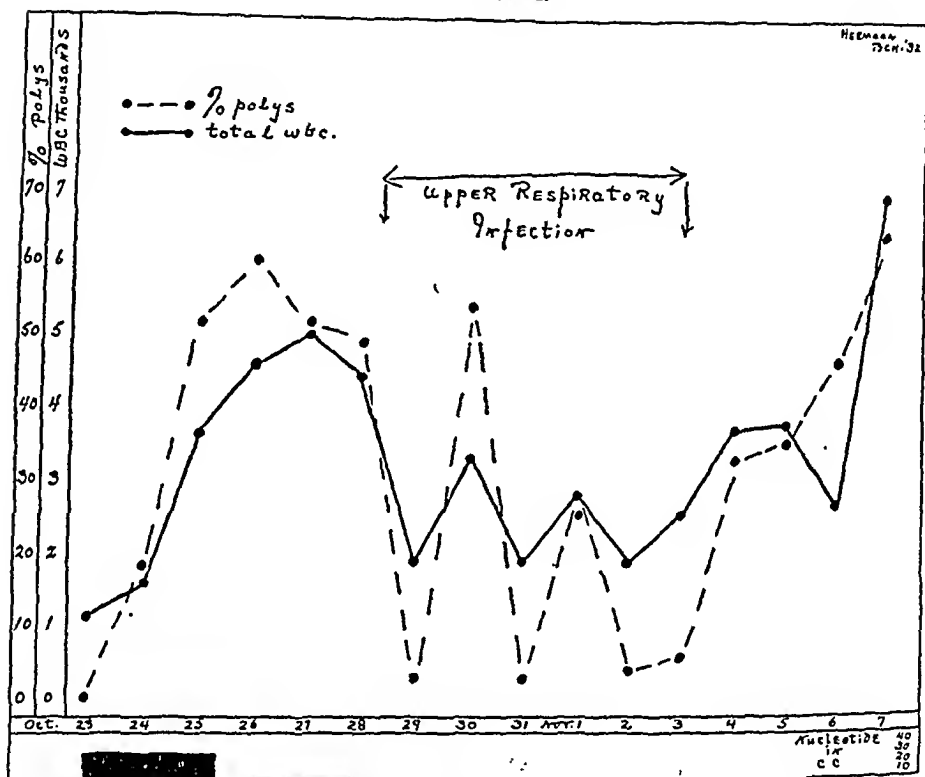
per c.mm. and it continued to rise during the succeeding days and the differential count of the cells became more and more normal. Preceding the rise in total white blood cell count there was a marked increase of young white blood cells,—stem cells, myelocytes and metamyelocytes. Mature polymorphonuclear neutrophils appeared only after the advent of those young cells. On December 26th she complained of much more pain in the rectum and perineal region and a small ischioanal abscess was found. Two days later this was opened and two



ounces of pus evacuated. Following the operation the white blood cell count abruptly fell to 3,700 per c.mm. although the polymorphonuclear neutrophils remained 69 per cent. On December 30th pentnucleotide was again started in 10 cc. intramuscular daily doses. By January 1st the white blood cell count had risen to 6,400 per c.mm. and the patient seemed much better. Uneventful recovery ensued.

The blood was very carefully followed after this attack and particularly so at the time of her menstrual periods. At the time of the catamenia a sharp

CHART 4.



drop in total count occurred and there was further a decreased percentage of polymorphonuclear neutrophils. Moreover, at each catamenia the total white blood cell count was found to be slightly lower than at the preceding one, although between periods it rose once more to an essentially normal figure. In September 1932 the white blood cell count fell to 3,000 per c.mm. with but 19 per cent. polymorphonuclear neutrophils. At the time it was predicted that the succeeding month would usher in another attack. This proved to be the case. On October 21, 1932 she had a slight chill and felt poorly. The next day she was better but on October 23rd she had a sharp chill, severe headache and general malaise. She was immediately brought to the hospital where her white blood cell count was found to be 1,100 per c.mm. (Chart 4.) No polymorphonuclear neutrophils were seen. The temperature was 102.5° F. Aside from marked asthenia and general prostration there were no particular symptoms.

No ulcerations were present. She was given 20 cc. pentnucleotide intramuscularly and thereafter 15 cc. twice a day for two days. The white blood cell count rose rather rapidly to 3,500 per c.mm. two days after entrance and the patient seemed much better—so much so that the pentnucleotide was omitted. The next day the white blood cell count was 4,500 per c.mm. and the differential showed 60 per cent. polymorphonuclear neutrophils, but the following day showed no further hematological improvement. The next day, October 28th, there was a slight fall in the white blood cell count and the day following the white blood cell count had dropped to 1,800 per c.mm. and the mature polymorphonuclear neutrophils had almost entirely disappeared. (Chart 4.) What explanation can we give for this sudden reversal of the picture? She had an acute upper respiratory infection with sneezing and a stuffed-up feeling in the nose. It is probable that this infection drained to its site all the polymorphonuclear neutrophils of the peripheral blood and that the only partially recovered bone marrow was unable to throw out cells fast enough to overcome the demand. It is interesting to note that the total number of lymphocytes and monocytes remained essentially normal—only the polymorphonuclear neutrophils decreased. Accompanying this infection there was a moderate rise of the temperature. Pentnucleotide treatment was resumed on October 28th and once more the white blood cell count started to rise and young granulocytes appeared, but an access of the upper respiratory infection on October 31st again brought the granulocytes to a low level without greatly disturbing the other elements. Again, however, young cells reappeared and after a slight set-back on November 2nd, probably due to an acute bronchitis, rapidly increased until on November 8th the white blood cell count was 6,000 per c.mm. with 60 per cent. mature polymorphonuclear neutrophils. The temperature was then normal and uneventful convalescence ensued. Intramuscular pentnucleotide was continued until November 5th when the great increase in young polymorphonuclear neutrophils and the marked improvement of the patient's condition seemed to warrant its discontinuation. It seems probable that the hesitant and intermittent hematological improvement was occasioned by intercurrent infections temporarily draining from the peripheral blood all the granulocytes which could be manufactured by the only partially recovered bone marrow.

This is a classical case of agranulocytic angina. Several points are to be noticed. First, she had had three typical attacks prior to the present two. From each she had recovered spontaneously. No specific therapy had been tried during these early attacks. The difficulty of attributing recovery to any given therapy is thus obvious. Second, the white blood cell count during the next to last attack was extremely low for two days before the onset of clinical symptoms. This argues strongly in favor of a primary leukopenia with secondary infection rather than the reverse. Third, during her fourth attack her white blood cell count started to rise definitely five days after the initiation of pentnucleotide therapy. In the great majority of cases it is about this time that definite hematological improvement occurs following this form of treatment, irrespective of the previous duration of the disease. In carefully studied cases, as has been pointed out above, stem cells, myelocytes and young polymorphonuclear neutrophils appear in increasing numbers after forty-eight hours of pentnucleotide treatment. (Doane.<sup>1</sup>) This was the case during the patient's fifth attack. Fourth, after the white blood cell count had risen and 69 per

cent. polymorphonuclear neutrophils were found there was a sudden drop on October 20th when the polymorphonuclear neutrophils virtually disappeared. Later, on November 2nd, a second reversal occurred, this time apparently occasioned by a tracheitis and bronchitis. Again after complete disappearance of polymorphonuclear neutrophils there was a flood of young cells and as the temperature fell and the complications cleared, the count gradually rose. In not a few cases after an initial rise of the total white blood cell count there may be a sudden fall. It is probable that in these instances an intercurrent infection is responsible for the drop in count. This was certainly the case during her fourth attack when there was an extraordinarily rapid development of an ischiorectal abscess shortly after the white blood cell had risen, and this complication was followed by a rapid fall of white blood cells in the peripheral blood. Such complications are not rare in agranulocytic angina and they require the usual treatment, irrespective of the underlying conditions. The development of pus at such a time is an indication of the patient's improved condition; it could not develop during the leukopenic stage. It must be regarded as a sequel to recovering bone marrow activity.

Agranulocytic angina occurs primarily in females. In our collected series of eighty cases 80 per cent. were in women. No age is exempt, but it appears to be most common in the early thirties and again in the fifties. It is distinctly rare in childhood. While the disease is by no means hereditary, yet in our experience more cases occur in relatives than can properly be ascribed to chance alone. In nearly 10 per cent. of our cases the disease occurred in two or more closely related siblings. It is possible that in certain instances some hereditary constitutional factor may predispose to the disease.

The etiology of the disease is unknown. Many authors (Brog-sitter<sup>2</sup>) regard it as merely an expression of an overwhelming sepsis. We cannot agree with this point of view. It must be admitted that one cannot, during life, always tell the difference between the leukopenia of overwhelming sepsis and that of true agranulocytic angina. Yet we believe the two conditions to be fundamentally different. Until the pathology of these conditions is better understood one cannot be certain.

In sepsis with consequent leukopenia as a rule obvious infection occurs before the fall in white blood cell count is manifest. In agranulocytic angina the reverse appears to be true, even though it may not always be apparent. Many, if not most, cases of this latter condition are seen so late in the course of the disease that accurate differentiation is difficult or impossible. There are few

reasons for doing a white blood cell count on apparently normal individuals. Yet patients with agranulocytic angina may be up and about and comparatively well with marked leukopenia. The case of agranulocytic angina summarized above, for instance, has a white blood cell count of 700 per c.mm. or less and a practically complete absence of polymorphonuclear neutrophils for three successive days before any other signs or symptoms were present. The patient felt perfectly well and was about her usual duties. Similar cases have been reported in the literature. (Connor.<sup>3</sup>) It is difficult to conceive of an infection which would bring about such marked hematological changes without at the same time causing some clinical symptoms. There are other points against infection being the primary causative factor. Individuals suffering from agranulocytic angina often have relapses and, furthermore, they may be subject to ordinary pyogenic infections and during these may, and usually do, respond in the normal manner with a leukocytosis. Such being the case, if we are to attribute the condition of agranulocytic angina to infection one must assume either some peculiarity of the host in its reaction to bacterial agents in general, or one must assume that some peculiar organism is causative. Yet the host cannot be constitutionally unusually susceptible to infections, except during an actual attack which is assumed to be the case, for many instances are recorded in which patients known to be subject to agranulocytic angina have passed through severe infections with a characteristic and marked polymorphonuclear leucocytosis. And again, it is difficult to adhere to the concept that there is a specific etiological organism for it is hard to understand how such an organism should again and again attack a given individual and why the victims should in the majority of instances be women. Furthermore, no such organism has been isolated either from the blood or tissues of those cases.

Certain cases have a more or less definite anaphylactic history, as has been noted by Pepper<sup>4</sup> in his excellent review of this general subject. Several of the cases in our series had been given serum or antitoxin just prior to the onset of the disease. Yet this may have been purely coincidence.

It would seem that the etiology of the disease must remain obscure but that, for the present, the best evidence points to some

recurring dyscrasia of the bone marrow of such a nature as to produce a primary leukopenia. Indeed, there is histological evidence that there is temporarily a paralysis of the white cell maturation factor. Very young granular cells are abundant and normal in the bone marrow; adult cells of this series are absent. Finally it should be noted that the disease is often initiated at the time of menstruation and some hormonal basis may eventually be found, but as yet the evidence in this respect is not clear.

The pathology of the disease is but little known. While many authors have described an aplastic bone marrow, we agree with Fitzhugh and Krumbhaar<sup>5</sup> that the essential lesion is a cessation of maturation of the granulocytic series at the myeloblast or myelocyte stage. In seven of our own cases (both treated and untreated) coming to autopsy, there was in the sternum neither bone marrow hyperplasia nor aplasia, but merely an arrest of white cell maturation. The bone marrow was of about the usual degree of cellularity. Red cell formation and the megalokaryocytes appear normal. Lymphocytes were somewhat increased in number—but the essential abnormality lay in the fact that none of the granular cells beyond the earliest stages were to be found. Indeed, the majority of this series were stem cells (myeloblasts) and from a morphological point of view these cells appeared quite normal and, paradoxically enough, in active mitosis. In keeping with this apparent paralysis of white cell formation in the usually active marrow a considerable degree of cellular hyperplasia was found in the normally fatty femur. Here the picture was essentially that of the sternum, showing that myelopoiesis to the stage of early myelocytes was active but that subsequent maturation was difficult or impossible. As Krumbhaar very aptly points out, there is a parallelism between this disease and another relapsing blood condition—namely, pernicious anemia. The pathology of the remaining organs is too little understood to be discussed at this time. One point, however, is of interest. In several patients who died of intercurrent infection the involved tissues showed at autopsy marked infiltration with polymorphonuclear neutrophils even though none were seen in the peripheral blood just prior to death. This finding substantiates our hypothesis that intercurrent pyogenic infections of a milder sort may bring about a temporary

fall of white blood cell count even though the marrow may be regaining its activity—as was indeed shown in these cases.

The symptoms of agranulocytic angina are legion. The onset is usually rapid, occasionally sudden. More rarely it may be described as ereeping. With this latter type of the disease the patient may have two or more minor attacks with chills, fever and malaise, lasting but a day or so and followed by complete good health for days or weeks before the disease sets in in earnest. This intermittency of onset is more apt to be seen in middle aged or elderly people and is incidentally rare in acute leukemia, a disease sometimes difficult to distinguish from agranulocytic angina. In acute leukemia the onset may, indeed, be insidious but as a rule the progress is continuous and not marked by complete clinical and hematological remissions.

Malaise is almost universal in agranulocytic angina and the asthenia may be very marked. Chills are common and may be severe. Headache, mental torpor and, more rarely, delirium may be seen. Generalized pains in the muscles, joints and long bones are complained of in some cases and are reminiscent of the occasional "rheumatic" pains occasionally seen in acute leukemia, especially in children. Abdominal symptoms are not rare—nausea, vomiting or diarrhea with tenesmus. Ulcerations of the mucous membranes occur in the majority of the cases. While they are most common in the mouth and nasopharynx, they may also be found quite characteristically in any part of the gastro-intestinal tract and may indeed involve almost any part of the body. In our series there have been ulcerations of the mouth, gums, pharynx, intestines, both large and small, skin, vagina and cornea and bladder. The ulcerations are probably to be regarded as the results of secondary infection in an already defenseless tissue. In the nasopharynx and throat they may be of great severity. Accompanying edema may cause dyspnea or dysphagia. Deeper ulcerations with gangrene may lead to erosion of large blood vessels and immediate death.

Jaundice occurs, but not often. Its pathogenesis is obscure. The spleen is frequently enlarged, but never greatly. A rise in temperature is almost always found sooner or later, although there may be relatively prolonged periods of leukopenia without fever,

if secondary infection is absent. The fever, which is in no way characteristic, may be continuous, intermittent or remittent.

Examination of the blood is of the utmost importance. Leukopenia is constant and indeed a *sine qua non*. The white blood cell count may fall to 1,000 per c.mm. or lower. Patients whose white blood cell count never drops below 2,500 per c.mm. can hardly be regarded as having the true disease in its fully developed form. It is probable, however, that as we learn more of this condition, abortive and mild cases will be more frequently recognized. Coincidentally with the fall in total white blood cell count the polymorphonuclear neutrophils drop to a very low level or actually entirely disappear. This granulopenia has been stressed in the literature and it is indeed most characteristic, but it must be remembered that there is also a marked decrease of the circulating lymphocytes. The normal total number of lymphocytes may perhaps be 2,500 per c.mm. yet in agranulocytic angina the total may well fall to 200 per c.mm. or even lower. The platelets are, as a rule, not greatly disturbed either in number or in character. This point may be of some importance in differentiating the condition from acute leukemia, in which disease they are usually greatly reduced, especially in the stages liable to be confused with agranulocytic angina. Anemia of a moderate grade is not uncommon in agranulocytic angina; more often the red blood cell count is approximately normal. Very rarely there is marked anemia of the hypochromic type, in contrast to acute leukemia which is always associated with progressive anemia which becomes pronounced. Eosinophils are very frequently absent from the blood of patients with agranulocytic angina even during the stages of remissions, and this fact may be of some diagnostic importance.

In the vast majority of cases of agranulocytic angina, the course is steadily progressive and death occurs in most untreated cases in a week or ten days. Occasionally the disease may be fulminant and a few patients of our collected series have died within forty-eight hours of the apparent onset. The word apparent is used advisedly, for it must be remembered that in certain cases, at least, the leukopenia precedes manifest symptoms and this leukopenia may have passed unnoticed for several days. In one case reported to us, however, no leukopenia was evident at the onset of symptoms

and yet the patient was dead within forty-eight hours. In the usual untreated cases the ulcerations spread, the fever and toxemia increase and the end is ushered in by bronchopneumonia. Not a few patients, however, recover from the initial attack and as the disease becomes better known it is not unlikely that more and more cases will be discovered to have suffered from a mild attack and recovered—at least temporarily. The tendency to relapse must, however, be constantly borne in mind. Then again, the patient may recover insofar as the hematological condition is concerned and yet die of some closely following complication. One patient recovered completely insofar as the blood condition was concerned but died a day later of massive infarction of the lungs.

There is another point concerning the course of the disease of the greatest practical importance and already alluded to. The leukopenia without question throws the organism open to bacterial infections of all sorts and not infrequently just as the white blood cell count has started to rise there appear, clinically, the outward and manifest signs of such an infection. Coincidentally, as in case 3, there may be a marked and sudden drop in total white blood cell count with perhaps a temporarily complete absence of polymorphonuclear neutrophils. Thus we have seen during early convalescence pyelitis, ischiorectal abscess, periappendiceal abscess and suppuration of the cervical lymph nodes. The hematological changes associated with these signs are not to be regarded as anything but the natural reaction of a slowly recovering hematopoietic system to an added strain. An ischiorectal lesion can exist in the presence of a marked leukopenia. Its outward and visible signs can become apparent only if the bone marrow can supply sufficient white blood cells. We are dealing with the laudable pus of our forebears. These complications require the usual surgical treatment which would be accorded the condition in any other patient.

So far there have been described only the classical acute form of agranulocytic angina. Variations from this type occur. In the first place there is the regularly recurring type of disease as described by Rutledge et al.<sup>6</sup> and Doane.<sup>1</sup> Then again there is what, for lack of a better term, may be described as the stuttering type. In these cases an acute attack may be followed by rapidly recurring, but very minor attacks over a period of many weeks or months. The



white blood cell count often varies within very wide limits from day to day without necessarily corresponding clinical symptoms. In our experience these cases are usually elderly individuals and it is not unlikely that chronic infection from some obscure focus in an individual with a poorly sustained bone marrow may not be causative. It is in these cases that pentnucleotide treatment is most disappointing.

The differential diagnosis of agranulocytic angina is sometimes easy, sometimes impossible. A number of diseases are associated with leukopenia. The majority of these need cause no confusion.

Typhoid fever, malaria, splenic anemia, pernicious anemia, benzol poisoning,—all may be associated with moderate or marked leukopenia. The symptoms common to these various diseases, as well as other more or less characteristic findings, serve as a rule to differentiate these conditions easily from agranulocytic angina or from the malignant leukopenia of sepsis.

There are, however, two conditions which may easily cause confusion. The first is idiopathic aplastic anemia. This disease runs a subacute or a chronic course. The anemia is progressive and in terminal stages extreme. Anemia is rare in agranulocytic angina. Leukopenia is usual in aplastic anemia and in general runs roughly parallel to the red blood cell count. In agranulocytic angina the leukopenia is uncomplicated by anemia. The differential count shows a relative increase of lymphocytes. The platelets are always reduced, often greatly so. The peripheral blood shows few signs of blood cell regeneration, even when the red blood cell count is at a very low level. In the later stages of the disease when the condition is most liable to be mistaken for agranulocytic angina, hemorrhages into the mucous membranes or skin are common in aplastic anemia. They are very rare in agranulocytic angina. Fever occurs in both diseases. A bone marrow puncture may have to be resorted to for a final diagnosis. In agranulocytic angina we have a bone marrow whose architecture is essentially normal and in which the cells representing the erythrocyte series are entirely normal. There is a cessation of growth, however, in the granular series at the myelocyte stage. No mature polymorphonuclear neutrophils are to be found. In aplastic anemia a variety of pathological conditions of the marrow

are found, often most difficult to correlate with the blood picture<sup>7</sup> but in none do we see the classical picture of agranulocytic angina.

The second disease for which agranulocytic angina may be confused is acute leukemia in the leukopenic stage and the distinction is of the greatest importance, both from a therapeutic and a prognostic point of view. This confusion is all the more likely to arise since ulcerative lesions in the mouth are common to both conditions. If painful and swollen gums have been present for several weeks without actual ulcerations the condition is probably leukemia. In acute leukemia there is usually a great reduction of platelets. This is not the case with agranulocytic angina. In acute leukemia, anemia is usually marked and progressive. Anemia in agranulocytic angina is rarely of any moment. In acute leukemia, especially in adults, there is a very considerable number of very immature cells. A few stem cells may be found in the blood of patients suffering from agranulocytic angina. Any very considerable number, however, indicates the liability of leukemia and the more there are the greater the liability is. A level is reached, perhaps 20 per cent., which if more than temporary almost certainly means leukemia.

Agranulocytic angina is rare in childhood; leukemia is not.

Leukemia patients with temperatures of 102° to 104° F. may seem comparatively well. This is not the case with agranulocytic angina. In this disease such temperatures are almost invariably accompanied by marked prostration and toxieity.

It should be emphasized that the total white blood cell count is of no vital importance in the diagnosis of leukemia. The character of the cells and the characteristic changes in the bone marrow determine the diagnosis. In the last analysis sternal bone marrow puncture may have to be resorted to.

Finally agranulocytic angina should be distinguished from the malignant neutropenia of sepsis, as pointed out above. This latter condition occurs about equally in the two sexes. It is not uncommon in children. In contrast to true agranulocytic angina the infection is the cause rather than the result of the leukopenia. This point is of the greatest importance in distinguishing the two conditions. Polymorphonuclear neutrophils with toxic degeneration are common in the neutropenia of sepsis. They are rare in true agranulocytic angina unless there be a secondary infection in the convalescent

stage. In the last analysis the distinction is somewhat academic; for the treatment, both local and general, is essentially the same in both diseases.

The specific treatment of agranulocytic angina and malignant neutropenia secondary to overwhelming sepsis is the same, although the two conditions appear to differ in their pathogenesis and in their pathology.

In the case of sepsis with malignant neutropenia, without local treatment of the local lesion, whether this be a sinusitis or a gangrenous limb, no hope of cure can be had. The lesion is the cause of the leukopenia. On the contrary the local lesions in agranulocytic angina cannot be permanently cured by local applications. They are dependent upon the leukopenia, not the cause of it. The constant therapeutic nudging of the patient with a variety of oral antiseptics served only to keep him awake when he should be asleep. General nursing care, however, is of the greatest importance, especially in regard to the skin, which must be kept scrupulously clean. Adequate sleep should be attained by narcotics if necessary. The coal tar products are commonly more useful than the opiates. Fluids should be administered freely. Mild, comforting gargles may be used. If food cannot or will not be taken by mouth, nutrient enemas may be necessary, but great care must be taken that there is no unnecessary irritation to the tissues. A close look-out must be kept for complications such as were mentioned above and prompt surgical intervention should not be delayed, if indicated, merely because the white blood cell count is low.

The specific treatment of malignant neutropenia, whether due to agranulocytic angina or to sepsis, consists in raising the white blood cells to a proper level.

Nonspecific protein therapy in the form of typhoid vaccine or sterile milk or leukocytic extracts appear to be of no permanent value. That recoveries have followed such treatment is not denied. That an increase of cells in the peripheral blood has followed such treatment is not denied, but this phenomenon is almost certainly merely a redistribution of cells rather than a renewed production. (Nye.<sup>8</sup>)

Transfusions of blood are advocated by many competent observers. In our opinion they often do more harm than good. It is again

not to be denied that patients have promptly recovered following blood transfusions. They have also recovered spontaneously. With increasing experience we have become more and more impressed with the dangers of transfusions in essential diseases of the bone marrow. We see no real indication for transfusions in agranulocytic angina. The life of the transfused white blood cell is notoriously short; there is seldom sufficient anemia to require transfusions of blood from this point of view and it has been our experience that in these cases there is, following transfusions, a marked and rapid fall in the white blood cells. Similar experiences have been had by Connor,<sup>3</sup> who cites a case in which the total white blood cell count was lower after transfusion than it was before. This phenomenon has also been noted following transfusions in other conditions. It is not peculiar to agranulocytic angina. Finally, we know of no direct evidence that blood transfusions stimulate hematopoiesis. The laity approve of transfusions and this therapeutic measure may, therefore, be unavoidable but our experience is that they are not curative. We advise against them unless there is a marked anemia.

Röntgen ray therapy over the long bones has been advocated chiefly by Friedman of Berlin. (Taussig.<sup>9</sup>) Other physicians have not had as much success. That x-radiation in heavy doses is harmful to bone marrow is well known, but while it cannot be assumed that very small doses used in treating agranulocytic angina are harmful, their beneficial effects have not yet been proved.

For many years it has been known that products of nucleic acid have the property of raising the peripheral white blood cell count (Doane<sup>1</sup>). Nucleic acid is a complex molecule made up of four nucleotides linked together. These nucleotides in turn are made up of a purine or pyrimidine base, a sugar, and phosphoric acid. In 1922, this author<sup>10</sup> first demonstrated clearly that nucleotides were a normal constituent of the body and circulated in no inconsiderable amounts in the human blood.

With these facts in mind it seemed not illogical to use these normally occurring complex chemicals as stimulants to white blood cell formation, or maturation, in these states accompanied by leukopenia, both peripheral and general.

Reznikoff in 1929<sup>11</sup> reported three cases of agranulocytic angina which recovered following the intramuscular use of salts of adenine

and guanine—purine bases derived from the more complete and more complex nucleotides. He has recently reported more fully on his work.<sup>12</sup>

In 1929 we began to treat systematically cases of agranulocytic angina and malignant neutropenia secondary to sepsis with pentose nucleotides. (pentnucleotide, N.N.R., formerly nucleotide K-96.) Our results have so far been encouraging<sup>13</sup> and have been confirmed and elaborated by Doane<sup>1</sup> and Mettier.<sup>14</sup>

In the usual case of agranulocytic angina or malignant neutropenia secondary to sepsis, 10 cc. of pentnucleotide are given intramuscularly twice or three times a day until the white blood cell count has definitely risen from its initial low point. Thereafter 10 cc. are given once a day until the white blood cell count has been normal for three successive days. In certain cases much larger doses appear to bring about beneficial results where the usual dose was ineffective. In extremely sick cases we give as much as 40 cc. a day in divided doses, continuing this large amount until there is definite improvement, both clinical and hematological. There would appear to be no advantage in intravenous administration, although we originally advocated it. Absorption from intramuscular administration is extraordinarily rapid. Pentnucleotide given intramuscularly usually produces no marked untoward reaction—there may be some local pain and not rarely there is nausea or vomiting shortly after the administration. Even more rarely there may be chills and fever several hours after the injections. These untoward reactions may usually be prevented by giving divided doses during the day. Thus, in one patient who habitually had rather severe reactions to 10 cc. we were able to give a total of 40 cc. a day without the slightest discomfort when 8 cc. were administered five times a day. We have also found it convenient in some cases to inject the material into a site previously anesthetized by 1 per cent. novocaine and adrenalin, the same needle being used for both injections. The present dosage is largely empirical. It is probable that the larger the daily dose the more rapid and the more sure the response.

No definite beneficial results are to be expected before the fourth or fifth day of therapy, although if the blood be carefully followed myelocytes will, in favorable cases, appear as early as the second day of treatment. Doane<sup>1</sup> has pointed out that there is a rise of *myelo-*

eytes in the peripheral blood prior to the marked rise of white blood cell count and we have also found this to be true in all of our personally observed cases.

On or about the fifth day after the initiation of treatment there is, in favorable cases, a sharp rise in the white blood cell count and mature polymorphonuclear neutrophils appear. It is at this time that the patient usually shows definite clinical improvement and the temperature rather abruptly falls to normal. Pentnucleotide treatment should not, however, be discontinued until the white blood cell count and the differential count has been normal at least for several successive days and treatment should be promptly resumed should there be a reversal, either in the patient's clinical condition or in the hematological picture. It must be emphasized further that following the initiation of pentnucleotide therapy there may be a further drop in total white blood cell count. This finding is to be attributed to the progress of the disease before treatment can sufficiently effect the production of white blood cells. It is in no way indicative of an unfavorable outcome and does not call for discontinuance of the drug, but indeed suggests a greater dosage.

As was pointed out above, septic complications are to be looked for in certain cases during the convalescent stage. They should be treated without reference to the underlying agranulocytosis. However, in respect to these complications there is another important matter to which we have previously alluded. Occurring as they do when the bone marrow is but just recovering it is not unreasonable to expect that the drain on the hematopoietic structures may be too great to maintain the improved and perhaps relatively normal peripheral blood picture. As a result there is not infrequently a sudden drop in or even a disappearance of polymorphonuclear neutrophils from the blood. This does not by any means indicate a recurrence of the disease. It is merely an indication of the fact that the bone marrow is unable to supply sufficient granulocytes to satisfy the need at the site of the infection. That this is actually the case is testified to by the fact that the other formed blood elements are not materially affected, but what few neutrophils are left usually show toxic degeneration, and by the fact that in cases dying with marked infection after four or five days of pentnucleotide treatment, yet the local septic lesions scattered throughout the body are amply

supplied with polymorphonuclear neutrophils. This secondary drop in polymorphonuclear neutrophils may be of very brief duration if the infection be a slight one or of longer duration if the complication is more wide spread or more virulent. In any event its appearance calls for a continuance of resumption of pentnucleotide treatment until the blood is once more normal.

Animal experimentation appears to support the clinical use of the material. Doane<sup>15</sup> found after seven daily injections of pentnucleotide a considerable hyperplasia of the bone marrow of rabbits and he also found after prolonged administration of the drug that there was new white cell formation in the spleen and, to a less extent, in the liver and kidney. This latter finding we have been able to confirm and amplify and we have found a new formation of white cells in the spleen as early as twenty-four hours after the first injection of pentnucleotide. At the same time a few myelocytes make their appearance in the peripheral blood. Thereafter this extramedullary myelopoiesis increases and appears to reach its maximum about the seventh day. Thus the animal experimentations support and confirm the clinical observations.

The published mortality for untreated agranulocytic angina is approximately 90 per cent., Doane.<sup>1</sup> To date there have been treated with pentnucleotide and reported to us ninety-one cases of agranulocytic angina or of malignant neutropenia secondary to sepsis and in this series the mortality is but 30 per cent. It must be remembered, however, that agranulocytic angina has a strong tendency to relapse and cases which have been successively treated once or even twice may finally succumb to a fulminating attack due to overwhelming infection invading a defenseless organism. The possibility of this eventuality necessitates a close follow up of these cases and we believe that pentnucleotide treatment should be at once resumed if the patient's white blood cell count drops materially, even though there are no symptoms, or if they have any infection, even though there is no drop in the white blood cell count. The wisdom of this policy is attested to by two recent cases, both of whom had been through one or more attacks. In the first case the patient, six months after her original attack, did not feel particularly well and developed a sore throat and fever. The white blood cell count was normal as was the differential count. Pentnucleotide

was immediately started. The white blood cell count progressively fell for several days and then on the fifth day of treatment rose again and the temperature fell to normal. In this instance we have an example of the fall of total white blood cell count during the first day or so of pentnucleotide therapy, with subsequent rise after therapeutic lag. The effect of the drug is not usually immediately apparent and those forces already at work may continue to hold sway until the favorable effect of the material is later seen. In the second patient, whose blood was being closely followed, it was found that her white blood cell count had fallen to 1,200 per c.mm. with but 2 per cent. polymorphonuclear neutrophils. She felt, however, perfectly well. Pentnucleotide was immediately started in divided doses. Young white blood cells appeared within twenty-four hours. On the fifth day the white blood cell count rose definitely and by the tenth day it was entirely normal. While it is utterly impossible in any given case to attribute a given result to the preceding treatment, the number of such cases in our series seem too large to be due to chance alone.

Many physicians seem to feel that patients with agranulocytic angina or malignant neutropenia from sepsis who have white blood cell counts above 1,000 per c.mm. or who have a few polymorphonuclear neutrophils in the blood, or those who have little fever, are apt to recover. We have been unable in our series to see any such correlation. In so far as our experience goes, neither very low white blood cell counts, nor complete absence of polymorphonuclear neutrophils, nor very high temperatures materially affect the prognosis.

There are, however, cases in which no response whatever is seen even when pentnucleotide is given in apparently sufficient amounts. There is some evidence at hand to show that in some of these cases at least the bone marrow does not show the classical picture of agranulocytic angina and the condition may be actually materially different. There are other patients who respond characteristically and in which the blood returns to normal, only to fluctuate subsequently in an erratic manner over a comparatively long period of time. As a rule, these cases respond at times to treatment, at other times not. Usually they get well eventually, but it is often difficult to ascribe their ultimate recovery to pentnucleotide. Similarly,



however, it is hard to say in retrospect what might have happened had no pentnucleotide been used.

However useful the drug may be in true agranulocytic angina and in neutropenia secondary to sepsis, it is of little or no value as far as our experience goes in aplastic anemia, nor is it of material benefit in leukemia, even though the white blood cell count be low. It is true that one individual suffering from acute leukemia made a remarkable recovery following the administration of pentnucleotide.<sup>16</sup> It is very unlikely that the treatment brought about the result.

In view of the fact that the differential diagnosis between these conditions and agranulocytic angina may be difficult, or impossible, what advice can be given in regard to pentnucleotide in these doubtful cases? If there be reasonable doubt as to the diagnosis, the wisest course would seem to be to administer the drug in full doses for a week or ten days and if at the expiration of that time no obvious benefit, either hematological or clinical, had accrued, to discontinue, at least temporarily, the injections. The same line of argument may be applied to patients with sepsis, without true leukopenia, cases in which one can merely say that the white blood cell count is not as high as one would expect or like. In one patient with a solitary abscess of the liver and a white blood cell count of 8,000 per c.mm. and a normal differential count, pentnucleotide was given and the white blood cell count rose to 32,000 per c.mm. The patient was operated on and recovered. It must be borne in mind, however, that in such cases the indications for pentnucleotide are not clear.

In summary, it may be said that there are two conditions associated with extreme leukopenia in which the leukopenia in and by itself is of utmost importance. First—sepsis followed by a lowered white blood cell count and diminished polymorphonuclear neutrophils and second—agranulocytic angina, a disease in which the infection is primary and the leukopenia secondary. The etiology and pathogenesis of the two diseases is probably different, the prognosis different. The treatment of either condition consists primarily in restoring the white blood cells to the proper level. This can be accomplished by the intramuscular administration of pentnucleotide (N.N.R.). In addition there

must be adequate nursing care and appropriate treatment of complications exactly as in any other patient.

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# INFECTIOUS MONONUCLEOSIS (GLANDULAR FEVER)

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UNDER the title of "*Infectious Mononucleosis (Glandular Fever)*" we shall deal in this article with several clinical pictures that have been described from three different standpoints. First, *Pfeiffer's glandular fever*, an infectious disease of children occurring in epidemics; second, sporadic cases studied from the standpoint of changes in the blood cells and described under various names (*infectious mononucleosis, acute benign lymphoblastosis, acute lymphadenosis, lymphatic reaction*, etc.); and, third, cases described from the standpoint of lesions in the throat (*monocytic angina, angina with lymphatic reaction*). There is a strong tendency at present among clinicians interested in the subject to unify these various pictures into a single clinical entity. This is based largely upon striking similarities in the morphology of the blood and other clinical features in cases of the three groups and upon adequately studied epidemics in which the various clinical manifestations come under the observation of a single competent observer.

Since the etiology is still unknown and the pathogenesis on a conjectural basis, it must be admitted that we cannot be sure whether there is needed a Laennec to unify the various clinical pictures into a harmonious whole as occurred with tuberculosis, or whether there should come a Louis to separate the various mononucleoses into their proper divisions as happened with the continued fevers through the work of the great French clinician and his disciples and the subsequent discovery of etiological agents.

The present trend toward unification may perhaps be better understood by a brief historical review of the subject.

In 1889, E. Pfeiffer, a physician of Wiesbaden, described a new symptom complex in children characterized by an acute onset during the best of health, pronounced fever, acute swelling of the lymph glands, especially behind the sternocleidomastoid muscle. The glands were very sensitive. There was swelling of the liver and the spleen.

There was slight catarrhal reddening of the fauces. After several days the fever declined but the glandular swelling remained for a longer period. Suppuration of the glands did not occur. He described both the epidemic and the endemic occurrence of the disease with notes of four cases in the same family. One of these cases was especially noteworthy in that it showed a relapse four days after the beginning of convalescence.

With the prestige of Henbner's support, Pfeiffer's communication was well received and during the next decade there were several corroborative reports of epidemics of glandular fever. In succeeding years, however, reports became fewer, more opposition developed to its acceptance as a clinical entity, and the syndrome fell into disfavor, more so in Germany than in England or in America. Queerly enough it appears that during more than thirty years no studies of the blood were recorded in any case that was diagnosed as glandular fever.

In the meantime there were isolated reports of cases with peculiar blood pictures, usually under the suspicion that they were instances of acute lymphatic leukemia. Such reports were made by Türk, by Hall, by Marchand, by Cabot, by Naegeli, and others. In 1918, there appeared an article by Deussing, describing a series of cases with a diphtheria-like angina and a lymphatic reaction in the blood. During an epidemic of diphtheria in Hamburg, he saw cases that were different from the usual ones with complaint of pains on movement of the neck, of headache and malaise. The pains were caused by fairly large lymphomas behind the sternocleidomastoid muscle. He described the inflammation in the throat, the general lymph node enlargement, the swelling of the spleen and of the liver, a red eruption on the trunk, an increase in the white blood cells with a marked lymphocytosis. One of the recent European reviewers, Nyfeldt, expresses regret that this excellent report should not have formed the foundation for further German work and that it was the Americans who in reality stood sponsor for the rebirth of Pfeiffer's glandular fever.

In 1920, Sprunt and Evans reported a series of six cases in young adults with fever, general lymph node enlargement, palpable spleen, increase in the white blood cells with a lymphocytosis including many pathological lymphocytes of different appearance, giving quite a

varied blood picture. They were of the opinion that these cases were examples of a definite infectious disease and they used the term "infectious mononucleosis." In 1921, Tidy and Morley described an epidemic and reported the first blood examination (with a lymphocytosis) in a case diagnosed "glandular fever." They were inclined to believe that the earlier described cases of "acute leukemia with recovery" and "infectious mononucleosis" were examples of the same disease as Pfeiffer's glandular fever. In 1922, Longcope contributed ten cases under the title of "Infectious Mononucleosis (Glandular Fever)." He felt that the condition could be differentiated from most other acute infections of known etiology and that the disease was probably due to a specific agent. He was inclined also toward a unity with Pfeiffer's glandular fever, a point that could not be settled at that time. The next year there were further reports on glandular fever in England by Tidy and Daniel, and in America an article by Downey and McKinlay on acute lymphadenosis compared with acute lymphatic leukemia especially notable for the excellent cytological studies and for their opinion that the disease described in young adults with acute tonsillitis or pharyngitis, absence of anemia, enlargement of lymphatic glands and frequently of the spleen, lymphocytosis, and comparatively rapid recovery of the patient, could not only be differentiated from leukemia but also from glandular fever with its highly epidemic nature, its occurrence in children, and the absence of tonsillitis or marked pharyngitis. In 1926, Baldrige, Röhner and Hansmann described an epidemic of cases similar to the sporadic type that had previously been diagnosed "infectious mononucleosis," supplying important support to the evidence that had already accumulated as to the identical nature of glandular fever and infectious mononucleosis.

In the meantime, in Europe, W. Schultz presented as monocytic angina a group of cases that were later published by Baader in 1922. In the German literature of the next few years there are many reports of angina with lymphatic reaction and of monocytic angina. It is interesting that later on Schultz himself with Mirisch agreed that the mononuclear cells in cases originally described as monocytic angina were really of lymphoid origin and that monocytic angina and angina with lymphatic reaction were one and the same condition.

In the years 1928 to 1930 the disease reached epidemic propor-

tions in several parts of Europe and it was carefully studied by Glanzmann in Bern, by Lehdorff and Schwarz in Vienna, by Nyfeldt in Copenhagen, and by Tidy and others in England. They were impressed by the similarity of the descriptions of cases reported respectively as glandular fever, infectious mononucleosis, and angina with lymphatic reaction. They noted in the same epidemic both in children and in adults cases with predominance in some instances of the glandular swelling, in others of the throat manifestations, and underlying them all the characteristic variable mononuclear blood picture. On these bases the authors mentioned are convinced that the conditions earlier reported from the various standpoints of an epidemic disease of children, of a sporadic infectious mononucleosis of adults, and of anginas with peculiar blood pictures, belong to one and the same clinical entity.

#### CLINICAL FEATURES

The sporadic cases affect older children and young adults. During epidemics many younger children become infected.

The symptomatology is highly variable. Obligate symptoms and signs are the febrile course, the enlargement of superficial lymph nodes, and the occurrence at sometime during the illness of the characteristic blood picture with increase in the number of lymphocytic cells and the occurrence of many pathological lymphocytic forms. These three important features are in themselves quite variable in their relative intensity and in the time relationship to each other. There are in each case additional symptoms including those due to the general toxemia with fever, to the pain and tenderness incident to rapid increase of the lymphatic swelling, to secondary infections in the throat and mouth, to pressure of the lymph swellings upon adjacent structures (the trachea, the bronchi, perhaps the bile ducts), to functional disturbances as of the gastro-intestinal tract, skin rashes, conjunctivitis, and less common complications (jaundice, hematuria). The additional symptoms greatly multiply the number of variants. This statement applies of course in some degree to practically all of the well-known infectious diseases, but in the disease under consideration there is definitely less than the usual conformity to an average in manner of onset, in the clinical course and in duration.

The typical case of glandular fever in a child follows a rather brief prodromal period during which there is evidence of fatigability. The child wishes to lie around instead of playing as usual, and may show irritability or restlessness, anorexia and constipation. The onset is fairly acute with rather high temperature. On the first day there may be no suggestive physical signs, or the lymph nodes may be enlarged. These have certainly appeared by the second or third day and may increase rapidly in size. In very young children, there is apparently little pain and not enough tenderness to handicap the examination. In older children, there is complaint of pain and tenderness that may cause stiffness of the neck and a turning of the head toward the direction opposite that of the chief swelling. Enlargement of the lymph nodes in other areas, the axillary, the inguinal, the epitrochlear, may soon follow, either at the same time or one after the other. The spleen may be palpable in the beginning or only after several days or may not be felt. The temperature remains elevated for several days and then falls by lysis. After the cessation of the fever the patient feels well but the glandular swellings disappear gradually and the blood picture may remain abnormal for weeks or for months. Tidy emphasizes his impression that after the fever is over there is usually a prolonged period of slight impairment of health and perhaps anemia that may require attention.

In the typical sporadic case of infectious mononucleosis the acute symptoms begin after a prodromal period of varying length. There may have been for a week feelings of easy fatigability, headache, constipation and general pains throughout the body and in the extremities, sometimes localized in one or more joints. Not unusually such symptoms may have persisted with variations in intensity for several weeks, and then the question arises whether the patient is not first seen in a relapse. During this prodromal period the temperature may have been slightly elevated. The symptoms become worse with increasing headache and malaise, with higher temperature and the patient takes to his bed. At this stage, the lymph nodes in the neck are usually palpable on one side or on both, and especially behind the sternocleidomastoid muscle. There may be palpable lymph nodes in other superficial regions or they may not appear until later. There is slight redness of the throat and perhaps some discomfort on swallowing. The spleen may be palpable on the first day but may not be

felt for two weeks or more. The general state of the patient is quite variable. He may seem rather miserable but not very ill, or the prostration may be quite marked, approaching a typhoidal state. Usually, when the patient first comes under observation, there are changes in the blood picture sufficient to lead to a strong suspicion of the correct diagnosis if not entirely definite. There may, however, be an initial leucopenia with a relative lymphocytosis. There may be in the beginning a slight polymorphonuclear leukocytosis that diminishes after several days and is replaced by the absolute increase in the lymphocytes. The change in the blood picture may occur over night.

In many of the sporadic cases the throat symptoms, mild or negligible at first, become very marked and may dominate the clinical picture. The tonsils become swollen and red with their crypts clogged with exudate, or there may be a pseudomembranous exudate over tonsils extending to the pillars, or ulcerative lesions suggestive of the Plaut-Vincent's angina. Many of the European reports are based upon the admission of such cases into hospitals for infectious diseases under the impression that they were diphtheria. Hence their emphasis upon the angina as the prominent feature of the illness.

The temperature may be continuously high at the beginning, or it may be irregularly remitting, or even of an intermittent septic type. Not unusually there is a rather regularly remitting temperature curve of moderate degree, the peak becoming lower each day after the third or fourth day and remaining normal after seven to ten days. A frequent and rather characteristic feature is the relapse. The fever may have subsided for several days to an almost normal figure, or the patient may have been afebrile for a period of days; then there is another rise of temperature, increased swelling of the lymph nodes with tenderness and a general increase in the symptoms. Usually the clinical features are milder during a relapse but may be the reverse. Where the patients are under careful medical observation, as are the medical students and nurses, it is not uncommon to have one of them admitted to the hospital suffering from a mild acute infection with perhaps some symptoms on the part of the upper respiratory tract, a few enlarged nodes in the neck, an indeterminate or mildly suggestive blood picture, and apparently recover or very



markedly improve after a few days. He is permitted to get up and leave the hospital. He may return to work but drags along with malaise, slight headache, and a week or two later, he is again admitted to the hospital with a typical case of infectious mononucleosis. Baldrige, Röhner and Hansmann have followed one patient through four attacks during three years.

After the fever disappears the patient's feeling of well-being rapidly returns, although the lymph nodes and the spleen remain palpable for weeks or for months and the blood picture may be quite slow in returning to normal.

So variable is the type of onset and the course of the illness in the same epidemic that Baldrige and his associates distinguished five separate types of onset and earlier symptoms. Glanzmann adopted their method and elaborated it considerably. Lehdorff is of the opinion that such detailed description of type is not justifiable and that for practical purposes the disease may be divided into two larger groups, namely, that in which the glandular swelling forms the chief clinical feature, the glandular fever as described by Pfeiffer, and the commoner type in most epidemics; and the group in which either from the first or at some time in its course the inflammation in the throat, the angina, dominates the clinical picture. He believes that perhaps a third grouping is justified to embrace those cases with rather high fever with only mild or moderate lymph node enlargement and with a blood picture showing many very immature cell types suggesting the stem cells and more closely approaching the picture of acute leukemia than does that of the average case.

#### DETAILED SYMPTOMATOLOGY

*Fever.*—Fever is an obligate symptom. There occur in epidemics very mild cases (*formes frustes*) in which the febrile period is not observed. Glanzmann recorded two cases from his large material with a persistent lack of fever.

The fever is of no definite or characteristic type. It may resemble that of sepsis or typhoid or may be so transient as to resemble febricula. As a rule the defervescence is by lysis but there may be a critical fall of temperature. The tendency to relapse and to recurrence has been noted above.

*The Lymphatic Apparatus.*—There is a general hyperplasia of the

lymphoid tissue throughout the body including Waldeyer's ring in the pharynx, the superficial lymph nodes, the adenoid tissue in the intestinal submucosa, the spleen, and perhaps also the lymphoid tissue in the salivary glands, in the liver and in other organs. Clinically, of course, there is no such universal recognition of lymphoid hyperplasia in any one case. It is recognized almost invariably in the throat and in the cervical region, particularly in the posterior triangles behind the sternomastoid muscles. Queerly enough, the left side of the neck seems to be most frequently affected. The size of the individual nodes as well as of the masses of nodes varies a great deal. They may be no larger than peas, or they may reach the size of a small orange. Usually there is little or no reaction in the surrounding tissue but there may be periglandular edema and possibly even some redness of the skin. With large nodes and with edema the swellings are readily visible and may form a large thick collar. The swelling may occur very rapidly. Tidy mentions an example in which there was little or no enlargement of the glands in the forenoon but a mass the size of a fist in the evening. The smaller nodes are firm and elastic in consistency; the larger ones are softer and may sometimes suggest suppuration but this is a very rare complication. The acutely enlarged nodes are usually tender and it would seem from the literature that they are more frequently tender as well as spontaneously painful in older children and in young adults than in infants from six months to two years of age. Movements of the head and neck may cause marked discomfort and the consequent rigidity and attitude may suggest the stiff neck of meningitis.

After those in the cervical region, the axillary nodes are next in frequency and in size of swelling. Not infrequently there is an axillary mass as large as a hen's egg. The nodes here, as in the cervical region, are usually discrete. The inguinal nodes are less commonly enlarged. The epitrochlears are frequently palpable.

Some authors speak of a *thoracic form* of the disease in which the peritracheal and peribronchial nodes show evidence of more marked hyperplasia than those elsewhere. Compression of the trachea with definite stridor has been described. There are a number of cases on record of pressure upon the bronchi with pulmonary signs of bronchial obstruction and with roentgen ray evidence of enlarged

peribronchial nodes. In this type there are described cases that may simulate whooping cough very closely, especially when the course is prolonged over two or three weeks. The lymphocytosis of whooping cough adds to the problem of differential diagnosis.

In the earlier literature of glandular fever much was written about enlarged *abdominal nodes* and of their detection clinically. Park West could palpate the glands in thirty-seven of his ninety-six patients. Haas found them frequently. Guthrie and Pessel considered palpable abdominal nodes rare. Glanzmann found them only once. They have been noted several times by surgeons in the course of laparotomies for supposed appendicitis. Uffenheimer, in discussing Scheer's paper, spoke of the suppuration of a mesenteric node with peritonitis and death.

The *spleen* is probably enlarged in all cases. Its clinical detection varies greatly in the statistics of different authors. In general it may be said that it is palpable in from one-half to three-fourths of the cases. Sometimes it is quite large. Usually the edge is near the costal margin and is firm and rounded. The time of the greatest splenic enlargement usually parallels that of the lymph nodes, but it may not be felt for several weeks after the beginning of the illness. On the other hand, the spleen may be palpable at the beginning and the general enlargement of the superficial nodes follow after several days. There is no parallelism between the severity of the disease and the size of the spleen. Chevallier records the occurrence of rupture of the spleen, its operative removal and recovery. Tenderness of the spleen and spontaneous pain in this region may be present.

Both the splenic enlargement and the lymph node swelling characteristically persist for weeks and sometimes for months after the patient is clinically well.

*The Blood Picture.*—Details of the blood picture will be considered in the section on hematology.

*Respiratory Apparatus.*—As in many other infections, *epistaxis* is not infrequently one of the symptoms of onset or occurs in the prodromal stage. The occurrence of *coryza* varies greatly in different epidemics and reports. There is usually a rather dry rhinitis and nasopharyngitis, or perhaps a mild serous exudate but rarely a mucopurulent coryza. There are cases with no apparent involvement of the mucous membranes of the nose or pharynx and there are all

transitions from this complete freedom from infection to the most intense inflammatory lesions. Baldridge and his associates reported reddening and injection of the mucous membranes of the pharynx without exudate in 58 per cent. of their cases. Scheer described a granular hyperplasia of the lymph follicles with small, peculiar, glassy, translucent nodes on the reddened pharyngeal wall. He considered this appearance characteristic in infants.

Pfeiffer did not consider the severer *anginas* as symptoms of his disease and they were not so described in the era before blood examinations were frequent. It is interesting, however, that a number of the earlier observers remarked the frequent co-incidental presence of severely inflamed throats in glandular fever cases. The severer follicular, pseudomembranous or diphtheroid, and ulcerous anginas are of more frequent occurrence in the sporadic than in the epidemic cases. They do, however, appear both in children and in adults during epidemics. There may be nothing in the appearance of the throat to differentiate such cases from the ordinary acute follicular tonsillitis or in the pseudomembranous types from diphtheria. The differential diagnosis is often made in the diphtheria wards of an infectious hospital. Almost all of Nyfeldt's series were discovered in this way. The tonsils may be intensely reddened and swollen. Membranes may spread from the tonsils to the pillars and to the palate and also to the posterior pharyngeal wall, but extension to the larynx is said never to occur. Nor do such membranes involve the upper pharynx or the nose. There are no croupy symptoms. The membranes vary in color and in consistency. Glanzmann described as characteristic for glandular fever a very smooth, almost a mirror-like surface of the deposit. It may be odorless or may have an odor like that of the malignant form of diphtheria. Bacteriological findings are varied and inconstant.

Retropharyngeal *abscesses* and suppuration in the glands of the neck do occur, but it is remarkable that with such tremendously inflamed throats secondary infections in the adjacent lymphoid tissue should be so rare.

*Cough* is a not uncommon symptom and there are a few reports of definite bronchitis and pneumonia as complications.

*Digestive Tract.*—*Anorexia* and *constipation* are frequent pro-

dromal symptoms and, among the children especially, *nausea* and vomiting. The nausea is usually of brief duration.

The tongue is heavily coated as a rule but shows no special or characteristic features.

*Stomatitis* is of frequent occurrence. There may be an erythema of the soft palate, sometimes going over on to the hard palate, usually a diffuse, sometimes a spotty reddening. Glanzmann speaks of small pimples most frequently on the palate but occurring in different places in the mouth cavity and sometimes coalescing to form larger plaques. He also described a fine granular appearance on the mucous membrane of the lower lip. Severe gingivitis and ulcerative stomatitis may occur.

Involvement of the salivary glands has been described and indeed spoken of as *glandular fever mumps*. English writers, especially Tidy, have been inclined to doubt its occurrence and to attribute such descriptions to confusion between swelling of the salivary glands and of neighboring lymph nodes with periglandular edema. Glanzmann, however, insists that involvement of both parotid and submaxillary glands does occur and described several cases during the epidemic in Bern. Scheer suggested that the glycosuria noted in one or two of the young children of his series might be due to a pancreatic involvement.

*Abdominal pains* at the onset or in the course of glandular fever are not rare. In his original report, Pfeiffer said that on the third and fourth day many patients complained of pain in the abdomen and especially in the midline between the umbilicus and symphysis. Later authors described the site of the pain as periumbilical or in the region of the liver or of the spleen or of the cecum. The time of its appearance is not constant. Definite pain in the region of the appendix may be an early symptom, as noted by Longcope and others. The intensity of the pain varies greatly but it may be quite severe. It is described usually as a colicky pain lasting for one or two minutes, with much longer intervals between the pains, during which the child may be quite comfortable. Tenderness may be general or it may be localized over McBurney's point or in the region of the gall bladder. Parkes Weber made note of a purely *abdominal form* of glandular fever without superficial lymph node swelling or enlargement of the spleen but with a characteristic blood picture.

There may be distinct enlargement of the liver, very frequently in children, less frequently in adults. In the epidemic among medical students described by Baldrige and his associates, liver swelling occurred in 16 per cent. Guthrie and Pessel encountered it much more frequently in their large epidemic among younger boys. It is usually attributed to hyperemia and parenchymatous swelling. The possibility of a lymphocytic infiltration is mentioned.

*Jaundice* occurs not infrequently in glandular fever and in infectious mononucleosis. It may be present in otherwise perfectly typical cases.

*Urogenital Tract.*—Glandular fever *nephritis* was mentioned by Heubner at the time of Pfeiffer's first description of the disease. In 1921, Tidy and Morley gave its frequency as 6 per cent. on the basis of cases collected from the literature. Guthrie and Pessel in hundreds of cases did not observe one with nephritis. Glanzmann saw it four times; Baldrige only once. This complication has not occurred among the cases in the Johns Hopkins Hospital. While it is spoken of as an acute hemorrhagic nephritis, Tidy regards it more as a pure hematuria. It usually comes on within the first week of the illness and is associated with few or no other symptoms suggestive of renal disease. Marked oliguria does not occur. There may be a few hyaline and granular casts. The prognosis is entirely favorable.

Glanzmann noted in small girls in the convalescent stage of glandular fever a striking *leucorrhea* that persisted for several weeks.

*The Nervous System.*—*Headache* is especially frequent and cerebral manifestations of the fever and general toxemia occur as in other infections. There may be a striking tendency to *somnolence*. In one of Glanzmann's cases encephalitis was suspected. Stiffness of the neck is not unusual as a result of the swollen, painful lymph nodes. Its presence may suggest the possibility of meningitis. Other signs of meningeal irritation may be noted, as in Longcope's case with slight stupor, hyperreflexia, and a positive Kernig. Epstein and Dameshek have reported a case with very marked cerebral symptoms, generalized lymph node enlargement, palpable spleen and typical blood picture with, in addition, a lymphocytosis in the cerebrospinal fluid. The patient recovered after an illness of three or four weeks. Johansen has described a similar case.

*The Skin.*—A great variety of skin *rashes* are recorded but there is none that can be considered characteristic of the disease. Among the most frequent are urticaria, erythema multiforme, a rash closely resembling that of rubeola, and others with a roseola suggestive of typhoid fever. Transient scarlatiniform rashes may occur. Skin hemorrhages are rare and in these exceptional cases the resemblance to acute leukemia is the more striking (Downey and McKinlay, Königsberger, Lewin, Williams). Petechial eruptions on the palate are more frequent than those on the skin.

The epidemic in England in 1930 produced many atypical cases with prolonged course, late development of lymph nodes, a palpable spleen, and a roseola exanthem that strongly suggested typhoid fever.

*The Special Senses.*—Symptoms on the part of the eyes are frequently observed. *Photophobia* may occur at the onset and a *dry conjunctivitis*, unilateral or bilateral, is not unusual.

*Otitis media* may occur as a rare complication.

#### HEMATOLOGY

The *red blood cells* are unchanged in cases of short duration. In those with a more protracted course there may develop a mild anemia of the secondary type. A point of occasional practical importance is the entire absence of nucleated red cells in the smears.

The *thrombocytes* are usually unchanged. There are, however, reports of marked diminution of the platelets in some cases, just as there is at times a hemorrhagic tendency. The rarity of these occurrences suggests that it is due to a complicating factor and is not a part of the disease itself.

The behavior of the polymorphonuclear *granulocytes* is variable. Sometimes when the case comes under observation the mononuclear blood picture is well developed and there is a mild or moderate reduction in the absolute number of granulocytes with a shift to the left in the nuclear picture and perhaps an occasional myelocyte. In other cases, especially in epidemics, there may be an initial polymorphonuclear leukocytosis that, after several days or perhaps several weeks undergoes a change with reduction in the polymorphonuclear cells and an increase in the lymphocytes. As cases are usually seen earlier during epidemics it is suggested that an initial polymorphonuclear increase is for this reason more regularly noted in epidemics than in

the sporadic cases. It seems unlikely, however, that there is an initial polymorphonuclear leukocytosis in all cases. It occurs not infrequently in sporadic cases and may persist for some days after there is distinct enlargement of the lymph nodes. Other cases with short prodromal periods and acute onset show the mononuclear increase from the beginning. Scherer emphasizes the initial polymorphonuclear increase in very young children. *Eosinophiles* are present throughout and may be moderately increased during convalescence.

The chief interest in the blood picture is centered in the *mononuclear cells*, including under this general term both lymphocytes and monocytes. Undoubtedly there occur in most cases numerous intermediary forms between the typical lymphocyte, on the one hand, and the typical monocyte, on the other hand, regardless of the method of examination or of staining. This has naturally resulted in confusion of opinions concerning cell derivations and about the nomenclature. American authors from the beginning have recognized the abnormal cells as of lymphoid origin. In Europe, the differences of opinion are apparently being clarified, aided greatly by the conversion of Schultz from the monocytic to the lymphocytic point of view. Naegeli and a few others are still inclined to separate cases into two groups according to the predominance of cells suggesting lymphocytic or monocytic forms.

By the use of the *supravital* method of staining, Sabin and Doan have stated without detailed descriptions, that each of them independently has studied the mononuclear cells in infectious mononucleosis and are of the opinion that they are lymphocytes. Wilson and Cunningham came to the same conclusion. Lawrence and Todd believe that on the basis of number and arrangement of neutral red granules alone the distinction cannot be made but that from other criteria, motility, cell outline and the character of the nucleus, it is evident that the cells are lymphocytes. European workers (Nyfeldt, Lorentz) who are perhaps less familiar with the method believe that it does not aid in the differentiation between lymphocytic and monocytic cells in this condition.

Downey's study of the cytology remains a classic. Schwarz has recently published a very full and detailed report of the hematology of glandular fever with many beautiful illustrations. He is in essen-



tial agreement with Glanzmann whose study is based upon a much larger material.

The total *white blood count* is usually between 10,000 and 20,000. Occasionally there are counts of 30,000 and rarely as high as 60,000 or 80,000. There may be a *leucopenia at the onset or at some time* during the course, usually at the expense of the polymorphonuclear leukocytes, but these are rarely below 2,000 cells per cubic millimeter. The mononuclear cells usually make up from 60 per cent. to 80 per cent. of the white blood cells, sometimes as high as 95 per cent. and occasionally as low as 40 per cent. More than half of the lymphoid cells may be classed as large lymphocytes and usually present some pathological feature besides their size. Monocytes are present in normal numbers or may be moderately increased.

The abnormal lymphoid cells may be pathological in regard to their *size*, in regard to the shape of the nucleus and its chromatin arrangement, and in regard to the structure and tinctorial properties of the cytoplasm. The *nucleus* may be round, oval, or even horse-shoe shaped, and is usually eccentric in position. The chromatin arrangement varies from the ordinary heavy chromatin bands of the lymphocytic nucleus to the finer and more regular network suggesting that of the monocytes. Or there may be a concentration of chromatin with a more radial arrangement like that in the plasma cells. Much more rarely, the nucleus is pale staining, with very finely divided chromatin and several nucleoli like that of the stem cell or lymphoblast. The important changes in the *cytoplasm* are the markedly increased basophilic tendency and the occurrence of vacuoles which when numerous may give the cell a foamy appearance. Another frequent type of cell has a much more uniform cytoplasm, a hyalinelike material, with few granules and much less basophilia. The European writers lay great stress upon the plasma cell tendency, distinguishing between true plasma cells with typical basophilic protoplasm and typical nucleus and the suggestive plasma cells (plasmazellig) with a marked basophilic protoplasm but without the typical nucleus. Cells with the pale staining nucleus with nucleoli and the darkly basophilic protoplasm they call lymphoblastic plasma cells.

Unfortunately, in most reports attention is paid exclusively to the differential count, distinguishing merely between large and small

lymphocytes, without descriptions of qualitative changes. Study of these qualitative changes may aid greatly in the diagnosis in atypical cases where the differential counts do not vary greatly from the normal.

Scheer gives the best description of the blood picture in very young children, from six months to two years of age, pointing out that at this age there is a normal preponderance of lymphocytes, making up from 50 per cent. to 75 per cent. of the white blood cells, over the polymorphonuclear leukocytes of which there are from 25 per cent. to 50 per cent. At the onset of the disease, he says, there is a marked increase in the polymorphonuclear leukocytes, followed after several days by a diminution in these cells and an increase in the large and pathological forms of lymphocytes at the expense of the small lymphocytes.

Although the pathological blood picture sometimes disappears with the clinical symptoms it usually lasts a very much longer time, paralleling more the duration of the lymph node swelling. It usually becomes normal within a few months.

#### PATHOLOGY

A decade ago the histology of extirpated lymph nodes in various stages of the disease was investigated by a number of observers. The findings in general were those of lymphoid hyperplasia with, in some cases, description of proliferation of the reticular cells and the endothelial cells of the sinuses. The capsules of the enlarged nodes were stretched and the peripheral sinuses full of cells but the capsules rarely invaded by cellular tissue. There were no inflammatory foci, no evidence of granulomata, and no areas of necrosis. Fox made the histological examination of a tonsil removed during an attack of infectious mononucleosis and found changes similar to those in the lymph nodes.

Owing to the great rarity of death from glandular fever or infectious mononucleosis there has been little or no opportunity for study of the general pathological anatomy. In the few cases that have come to autopsy death has been considered to be due to secondary infection. Park West reported the death of a child who was in very poor condition before the onset of this disease. Bellotti noted a fatal termination in two cases, children aged one and a half and three

years, respectively, after the glandular swelling had subsided and following a subsequent cachexia. Korsakoff reported the death of a five year old boy with an autopsy. In this case death was due to a secondary infection with the streptococcus and a general sepsis. There was general hyperplasia of all the lymphatic tissue in the body and a glomerulonephritis. Haken reported the death with autopsy of three children from monocytic angina. The autopsies showed evidence of general sepsis. Königsberger, however, took sharp exception to his report and insisted that the cases were examples of malignant diphtheria. DuBois in an autopsy of a case complicated by pneumonia and empyema was impressed with the evidence of hyperplasia of the reticulo-endothelial system and regarded this system as the source of origin of the pathological cells in the blood. Bass and Herman observed a boy nine years of age who had for some time been ill with a nephrosis. He passed through an ordinary attack of infectious mononucleosis and fifteen months later, when all signs of this disease had disappeared, he died of the nephrosis. The autopsy was entirely negative in so far as the lymphatic structures were concerned.

#### ETIOLOGY

The etiology of the disease is unknown. Blood cultures are almost invariably sterile. Cultures from excised lymph nodes are usually sterile. Baldridge, Röhner and Hansmann found a diphtheroid organism in lymph nodes and in the blood but considered them secondary invaders. Injections of the blood or lymphoid tissue from patients into animals has in the hands of most experimenters been negative. A great variety of organisms has been found in the pharynx and anginal membranes, including different strains of streptococci, influenza bacilli, diphtheroid organisms, the fusiform bacilli and spirochetes of Vincent, avirulent diphtheria bacilli, and very rarely virulent diphtheria bacilli. These are accepted by most commentators as secondary invaders. Streptococci are usually responsible for the suppuration in the very rare retropharyngeal abscesses and suppurating lymph nodes.

The frequent occurrence of the fusospirochetal group of organisms in the inflamed throat of infectious mononucleosis has led a number of observers (Schmerel, Zikowsky, Fr

Elkeles) to attribute to these organisms an etiological role in the general disease, but only Gorham, Smith and Hunt have furnished any experimental observations in support of this hypothesis. There are many cases of infectious mononucleosis without lesions in the throat and in which many examinations for these organisms are negative.

Nyfeldt has reported the finding of a small, non-motile, slow growing bacillus in blood cultures on special media and the production of a mononuclear blood picture in rabbits by the injection of this culture. He states, too, that the organism is agglutinated by the serum of the convalescent patient. He named the organism the *Bacillus monocytogenes hominis*.

Bland was unable to confirm this observation, using the same method. He reports, however, by injecting patients' blood into rabbits, the production of a fatal disease characterized by high fever, anemia, a mononucleosis, rapid cachexia, and death in eight or ten days. The rabbit's blood in turn is infectious for other rabbits and he reports further that by injecting the rabbit's blood into monkeys he could produce a disease that closely resembles the glandular fever of man. Lehdorff received some of the infected rabbit's blood from Bland and was able to confirm his findings in so far as they pertained to transmission to rabbits. Bland believes that the experimental disease in rabbits is brought about by a protozoan of the genus *toxoplasma*.

#### INCIDENCE AND EPIDEMIOLOGY

The disease has been described in the temperate zones of North America, Europe and Australia. There is a definite age incidence, sporadic cases affecting older children and young adults. In epidemics there are many younger children. Infants up to six months of age with rare exceptions seem immune. Few cases are found above thirty years and still fewer above forty. Boys are more prone to the development of the disease than girls.

Sporadic cases of infectious mononucleosis, according to available statistics, are relatively rare but there is reason to believe that the disease is much more common than published reports would indicate. The fact that such a large proportion of the cases in a teaching hospital occurs among the medical students, nurses and

resident staff may be explained by the fact that only in this class of the population do relatively mild cases come under hospital observation. They are under careful medical supervision, the hospital is their infirmary, and when sick even with relatively minor infections they are admitted to the hospital as patients. Other cases that come under careful observation are the very severe ones with throats resembling diphtheria or with protracted course suggesting typhoid or sepsis, or with blood examination indicating the possibility of leukemia. Many cases may pass under the guise of influenza, the grippe, or an upper respiratory tract infection.

The sporadic cases show little if any evidence of direct contagion, yet there are notable exceptions where sweeping epidemics in boys' schools have resulted apparently from a sporadic case among the teachers.

Most of the *epidemics* have occurred in schools, in children's homes, in barracks, or else as small, scattered house and family epidemics.

In contrast to the lack of contagion in sporadic cases, the susceptibility to infection in epidemics is quite general. Among young children Davis reported 100 per cent. infected of those that were exposed. In Scheer's epidemic, 60 per cent. of the exposed became ill and many of those that remained well were less than six months of age. In epidemics among older children and young men the incidence of infection is somewhat less.

Among the points raised against the idea of the identity of sporadic infectious mononucleosis of young adults and the epidemic glandular fever of children are the great difference in contagion and the somewhat different clinical features of onset and course. In his careful study of the Bern epidemic Glanzmann emphasizes the occurrence of contagion from children to adults and from adults to children and the striking similarity in the course of the disease regardless of age.

The *incubation period* is given as four days by Scheer, five to eleven days by Pfeiffer, seven to eight days by Tidy and by Glanzmann, and ten to fifteen days by Tidy in later epidemics. Scheer emphasizes that the infection spreads from one child to the child in the next bed and that fairly close contact is necessary. Droplet infection is the supposed method of transference.

Haberfeldt, in Brazil, has described a similar disease of the glands and of the blood in field workers as the result of tick bites. This suggests the possibility of a protozoan infective agent. No evidence has been adduced that the disease is transmitted by insects in the countries of North America or of Europe.

Several epidemics of glandular fever have followed in the wake of other diseases, notably measles, German measles, scarlet fever, and influenza. According to current opinion, epidemics of glandular fever may be expected in a community much less frequently than measles and with about the same degree of frequency as German measles, approximately once in a decade.

#### PATHOGENESIS

One of the views of the pathogenesis that has recurred throughout the history of glandular fever and is well exemplified in such a term as "angina with lymphatic reaction" is that the lymphoid swelling and lymphatic blood picture are due, not to any special invading agent, but to a peculiar reaction of the infected individual, to a "lymphatic constitution." Whether such a lymphatic constitution exists or not, and regardless of the fascination of constitutional doctrines, the evidence in this instance is overwhelmingly against such a view point and in favor of a special infective agent or virus peculiar to this disease. On the one hand, we have the general susceptibility to the infection of those who are exposed in epidemics, and on the other hand, the many cases now in the literature that, before or after the attack of glandular fever or infectious mononucleosis, or both before and after, showed a polymorphonuclear leukocytosis in response to a common infection like acute appendicitis or acute tonsillitis.

It is assumed that the virus comes into the body by means of droplet infection, by kissing, or barely possibly by means of food, and that the portal of entry is the upper respiratory tract in most cases and perhaps the gastro-intestinal mucous membrane in a few cases. It is apparently a general disease. It does not involve the regional lymph nodes but the lymphoid tissue all over the body. The essential features, besides the fever and other toxic manifestations, are the marked hyperplasia of the lymphatic tissues and the entrance into the blood stream of abnormal lymphoid cells.

It is pointed out that there are other such infectious agents that may be spoken of as lymphotropic viruses that cause diseases with somewhat similar characteristics, especially whooping cough with its very marked lymphocytosis (though usually made up of the small lymphocytes), rubeola or German measles with the lymph node enlargement, sometimes a palpable spleen and the plasma cell blood picture, and acute lymphatic leukemia with the fever and other toxic manifestations, the general lymphoid hyperplasia and the outpouring of immature and pathological lymphoid forms into the blood stream.

Schwarz especially insists that the differences between infectious mononucleosis and acute lymphatic leukemia clinically, pathologically and hematologically are those only of degree and not of kind.

Not the least remarkable among the features of infectious mononucleosis is the fact that, although this disease in its worst form may cause a severely prostrating illness, when uncomplicated it has apparently never produced death. Even with the many secondary invaders in the throat that are favored, according to some authors, by the diminution of the granulocytes in the blood and with the rare penetration of streptococci into retropharyngeal tissues and cervical lymph nodes, fatalities have been extremely few. Not only is there a remarkable resistance to the primary disease but also to its usual complications. Can it be that peculiar immunological reactions, as indicated by the presence of heterophile antibodies, safeguard these patients' lives?

#### DIAGNOSIS

The diagnosis is a purely clinical one based upon the three important features, *fever*, *general lymphatic hyperplasia*, and the peculiar, variable *lymphocytic blood picture*. The presence of other less important, but still frequently occurring, symptoms and signs is helpful.

In the absence of a known etiological agent, an etiological diagnosis is of course impossible. Until recently, no immunological reactions peculiar to this disease were known. The recent demonstration in infectious mononucleosis of heterophile antibodies that seem to be lacking in possibly confusing conditions is a highly promising development.

The diagnosis is quite readily made in the typical case by one who is familiar with the disease. Less typical cases may be quite

confusing, especially when the characteristic blood changes have not appeared. The presence of an initial polymorphonuclear leukocytosis is not merely of negative value but may naturally be positively misleading. The repeated examination of the blood with careful study of the qualitative as well as of the quantitative changes is sometimes necessary before the diagnosis can be established.

In the *differential diagnosis*, consideration must be given, first, to other acute infectious diseases, and second, after the febrile stage and during convalescence, to other causes of general lymph node and splenic enlargement.

Of general infections that perhaps come most frequently to mind there are influenza, the grippe, typhoid fever, and, as Glanzmann emphasizes, rubcola or German measles. Mumps may be suspected if the glandular swellings are so placed as to simulate enlargement of the salivary glands, or in the rare cases where these glands themselves are involved. Whooping cough may occasionally be considered in the thoracic form of the disease.

In cases with marked throat involvement, diphtheria, scarlet fever, the Plaut-Vincent's angina, and agranulocytic angina may come in question. From these infectious mononucleosis (glandular fever) may be distinguished by a careful study of the blood smears as well as by the bacteriological and other special diagnostic methods of value in the various diseases. Besides the blood picture the general nature of the lymphatic involvement and the presence of a palpable spleen are helpful in determining the secondary nature of the throat infection during the course of a case of glandular fever. Another helpful feature is the frequent late occurrence of the throat manifestations after the patient has definitely been ill for several days.

In the later stages of persistent glandular enlargement and mild splenomegaly, the differentiation from Hodgkin's disease, from tuberculosis, and from syphilis is usually not difficult on the basis of the history, the physical examination and the blood picture. A biopsy of a lymph node may occasionally be required and the histology is quite different from that of the granulomata.

In regard to the general infections first mentioned, particularly influenza and the grippe, the difficulties may be great in mild cases of glandular fever with little lymph node swelling and a poorly



developed blood picture. Especially may this be true in children. More thorough studies of the blood picture in the influenza of childhood may be helpful in making this differentiation more satisfactory than it is to many pediatricians at present.

The epidemic of glandular fever in Switzerland followed one of rubeola and Glanzmann was impressed by the similarity of these two diseases. Both are associated with enlarged lymph nodes especially in the neck; both show a lymphocytic blood picture with the presence of plasma cells; the characteristic eruption of rubeola may be absent in certain cases of that disease and a very similar eruption may be present in some cases of glandular fever. So much impressed was he, that Glanzmann was inclined to advocate the removal of rubeola from the list of the exanthemata and to classify it as one of the diseases caused by a lymphotropic virus. Important differential points are the less extensive glandular swellings in rubeola that are confined as a rule to the occipital or posterior group of glands with rarely swelling of the other cervical glands, and still more rarely those of the axillae and inguinal regions. The spleen is usually not palpable or is barely so. The lymphocytosis in rubeola is of much lower degree than in glandular fever and the percentage of typical plasma cells is higher in rubeola, which moreover lacks the variable lymphocytic blood picture characteristic of infectious mononucleosis.

It is well to keep the possibility of glandular fever in mind in the diagnosis of acute abdominal conditions, especially if there are atypical features.

Cases with more gradual onset with increasing fever, epistaxis, throat infection, lymph node and splenic enlargement, and a peculiar blood picture may give rise to fear of an acute lymphatic leukemia. This has happened very frequently in the past, especially before the disease came into general recognition. In the great majority of cases expert hematologists will have no trouble in making the differentiation from the blood smear alone. The total white count and the general terms of a differential count may be quite similar in the two conditions. The absence of anemia, the absence of nucleated red cells, and the presence of only a very few undifferentiated or immature lymphocytic cells when judged by the character of the nucleus are valuable points in the differential diagnosis of the blood smears of an infectious mononucleosis from acute leukemia. The variability

of the lymphoid cells in infectious mononucleosis is another helpful feature. The great majority of the lymphoid cells in infectious mononucleosis are not immature or undifferentiated cells but vary from the normal lymphocytes in other particulars. The great rarity in glandular fever of a thrombocytopenia and a hemorrhagic tendency is a helpful differential point.

In the course of a study on the occurrence of *heterophile antibodies* in clinical conditions as determined by the presence of agglutinins and hemolysins for sheep's red blood cells, Paul and Bunnell found these nonspecific antibodies in very high titer in the blood serum of cases of infectious mononucleosis, in considerably higher titer in fact than in cases of serum disease, another condition with which they are associated. Sheep cell agglutinins occur in normal and in general hospital patients in very low dilutions of the serum of 1-4 or 1-8 in a fairly high proportion of people from five to twenty years of age. They very seldom occur in dilutions higher than 1-32, except in serum disease where they are found in dilutions of 1-64. In four cases of infectious mononucleosis, Paul and Bunnell found them present in dilutions of 1-128 and in one case in a dilution of 1-1000. No more than the usual amount was found in lymphatic leukemia, in Vincent's angina, or in Hodgkin's disease. There was one peculiar case considered probably an aplastic anemia in which the titer went up to 1-128. The titer of the agglutinins in infectious mononucleosis was higher in the acute stage of the disease, gradually diminished and disappeared before the blood count became perfectly normal. During the past year, in the Johns Hopkins Hospital, Bernstein has examined seven definite cases of infectious mononucleosis and found in all of them this heterophile antibody in high dilutions of the serum. In one suspected case of the abdominal type of infectious mononucleosis, a case in which the hematologist was not entirely satisfied from examination of the blood smears, the test was negative. Among the large number of other patients examined, one case with thrombocytopenic purpura showed the agglutinins for sheep corpuscles in high dilution but they disappeared from the blood much more rapidly than did those in the cases of infectious mononucleosis. Gorham has also examined the blood serum of seven cases finding high titers of the agglutinins in all of them. If this earlier work is confirmed in larger series of cases it should be a most

helpful diagnostic procedure. The test is very simply performed in small test tubes, using a 2 per cent. suspension of sheep's red cells and various dilutions of the inactivated serum of the patient.

The false positive Wassermann reactions that have occasionally been noted in patients with infectious mononucleosis by several observers (Parkes Weber, Lehdorff, Rabaut, Chevallier) may in some way be related to the presence of such heterophile antibodies. If their uniform occurrence becomes definitely established in sporadic infectious mononucleosis, great interest will attach to the presence or absence of these heterophile agglutinins in cases of a typical epidemic of glandular fever among children.\*

#### PROGNOSIS

The prognosis is uniformly favorable. Fatalities and unfortunate sequelae have been so rare that practically they may be disregarded. This is one of the important reasons for making the diagnosis early for the favorable prognosis can be given as soon as the diagnosis is made.

The course and the duration of the illness cannot with certainty be predicted and the frequency of relapses must be kept in mind.

#### TREATMENT

In the average case the treatment may be that of any acute febrile illness of brief duration. The patient should remain in bed during the febrile period, he should have a bland diet and an abundance of fluids.

In addition to the general measures the treatment consists chiefly in combating individual symptoms. The tendency to constipation will require attention. Both warm and cold applications have been advocated for the pain and tenderness in the lymph nodes. The milder analgesics may be useful and codein is indicated if the discomfort is marked. When the lymphoid masses are large and soft,

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\* Since this paper was completed there has appeared an article by Rosenthal, N., and Wenkebach, G., of New York, in the *Klinische Wochenschrift*, 12:498, 1933. They find the heterophil agglutinins present in infectious mononucleosis and absent in some conditions that resemble it, but their conclusion that the test is negative in glandular fever, thus separating glandular fever from infectious mononucleosis, seems hardly to be borne out by the accompanying case reports.

with periglandular edema, Glanzmann advocates the use of local ultraviolet radiation.

Many different measures have been used in treating the throat complications. When the fusospirochetal group of organisms is present, the local application of neoarsphenamine Gm. 0.15 in glycerin 10.0 is suggested. Irrigations of the throat with warm cleansing solutions of sodium perborate or potassium permanganate are helpful. In the rare cases where virulent diphtheria bacilli are present in the throat diphtheria antitoxin should be administered promptly. This is often done as a routine procedure on admission into a diphtheria ward and several authors have noted that the serum has seemed helpful even in the absence of diphtheria.

No strenuous therapeutic measures are necessary in the great majority of cases and they are usually inadvisable (arsphenamine and mercurochrome have been used intravenously). Nucleotides have been used without obvious benefit.

When a patient has suffered several relapses or the course of the illness is much prolonged, a transfusion of blood from a donor who has recovered from the disease or from a healthy adult may serve to cut short the illness.

During convalescence tonic measures should be instituted for any impairment of health or mild anemia.

The question of the isolation of patients always arises and is variably answered. The sporadic cases are rarely dangerous, even to children in the same family. During epidemics, patients should be separated in cubicles, their dishes and utensils should be sterilized and the attendants should observe the precautions usual in a ward for infectious diseases. It would seem wiser also to isolate the sporadic cases since it must be from them that epidemics take their origin.

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# PELLAGRA: A RÉSUMÉ

## With Special Reference to Etiology

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THE current knowledge of pellagra, if it could be applied, is probably adequate to prevention of the disease, but is inadequate to its cure in many cases at the time they come under treatment. To justify this statement and to review some of the more important aspects of the subject will be the purpose of this paper.

A large element of personal opinion has characterized most of the literature concerning pellagra. Bigland and Enright held divergent views of etiology though they worked in the same environment. Each dealt with prisoners of war in Egypt, Bigland with Ottomans and Enright with Germans. More recent are the statements of two collaborators, Thatcher and Sure. Sure<sup>1</sup> wrote in 1933: "That pellagra is a disease caused by a deficient diet has now been fully established by the work of his co-workers." Thatcher<sup>2</sup> stated: "The most important factor in the etiology of pellagra is a deficient diet. It is a dietary

serves well stated: A sixty years the cause he disease eory that ly to the t present factors, or cane The sig- ace, be-

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cause of the seasonal variations noted in lesions of the experimental animals suffering from lack of the antipellagrie vitamin; also because a fungus having fluorescent properties has been isolated from the stools of pellagrins. Thatcher further thought that there is importance to the possibility that an organism is the causative factor in pellagra.

The idea of a food deficiency as related to pellagra dates back to the earliest descriptions of the disease. As the Goldberger-Wheeler school have advanced their postulates of a deficiency of protein or of an amino-acid, and finally of a vitamin, there have been dissenting opinions all the way along. These have taken a range from nice distinctions to outright contradiction. Thus Enright,<sup>3</sup> in 1920, concluded that, while he did not mean to suggest that a food deficiency could be quite excluded, from the facts before us it could hardly be considered as of paramount importance.

Mitchell,<sup>4</sup> in 1924, thought that, while it is clearly established that dietary error or errors of some kind are primarily responsible for pellagra and that the presence of certain amounts of protein-rich animal foods, particularly milk and meat, in the diet is an effective preventive against this disease, the disease has not been definitely traced to deficiency of protein or amino-acid, "even though the arguments of the proponents of this deficiency theory are granted *in toto*."

Taylor,<sup>5</sup> in 1930, was inclined to regard an infectious agent as also operative, but he did not question the importance of a deficiency of food.

Turner,<sup>6</sup> as recently as 1931, thought pellagra almost unique among the major diseases in the scarcity of accurate information concerning it. He characterized the etiology as uncertain, the pathology obscure, the diagnosis of atypical cases as a matter of mere opinion, and the prognosis and cure as lacking any adequate criteria.

Spies,<sup>7</sup> in 1932, reported five cases of pellagra in which the skin lesions improved strikingly while the patients were receiving a diet believed to be lower in protein content and in vitamins C, D and G than so-called pellagra-producing diets.

Nevertheless, it may be said with reference to the United States, that the theory of pellagra now accorded more general recognition than any other and the theory with most to its credit in practical results, is that of the Goldberger-Wheeler school. Though there are



In a series of hospital cases reported in 1932 by Boggs and Padget<sup>9</sup> from Baltimore, the mortality under the most favorable method of treatment (liver diet) was 19.5 per cent. in uncomplicated cases.

In a series of hospital cases reported in 1931 by Turner<sup>6</sup> from New Orleans, the mortality was 31 per cent. "in spite of treatment," (dietary and symptomatic) "along the most approved lines."

#### PATHOLOGICAL

As regards structural changes, Thatcher's<sup>2</sup> review is reproduced in abstract. The anatomical lesions are related chiefly to the skin, nervous system and digestive tract, and are similar to those of senility.

The skin lesions are strikingly symmetrical and tend to affect exposed surfaces, though not exclusively. The early stage is represented by vascular injection and edema of the corium with a diffuse infiltration of wandering cells. Later edema and hyperplasia of the rete with regions of parakeratosis appear. Hyperkeratosis and hyperpigmentation are present as the malady advances, (MacNeal).

Degenerative changes characterize the nervous system and may involve the various columns of the spinal cord, spinal and sympathetic ganglia, medulla and cerebrum, including early sclerotic changes in the arteries of the brain even of young people.

The red and inflamed tongue often ulcerates, with similar changes in the lips, gums and buccal mucous membranes. Hyperemia, inflammation and repair of the upper gastro-intestinal tract and of the colon are observed.

Changes in Metabolism: The chief features of the metabolism of pellagra,<sup>10</sup> many of which are proportional to the severity of the disease, are as follows.

The general metabolism, as measured by the consumption of oxygen or the excretion of carbon dioxide, is low, though no impressive series of observations as to the basal metabolic rate has been noted in the literature.

The exogenous and endogenous metabolism, as measured by the urinary excretion of nitrogen fractions, is low.

There is an abnormal mineral metabolism, as is evidenced by a low excretion of phosphorus pentoxide. Serum calcium is at times abnormal, and possibly may be correlated with mental symptoms.<sup>11</sup>

The utilization of protein is regarded as being somewhat depressed,<sup>10</sup> though the observations made in Egypt did not indicate this.

There is a decrease in the thiocyanate contained in the saliva, but the normal diastatic power of the saliva is average.<sup>12</sup>

Gastric anacidity and absence of pepsin is common, and hypacidity is usual.

Intestinal putrefaction is increased<sup>10, 13</sup> but the phenols in the urine were not found to be altered quantitatively.<sup>14</sup>

Total blood volumes for 17 per cent. of the pellagrins examined were above ideal values and 82 per cent. were below ideal values.<sup>15</sup>

The cholesterol content of the blood is increased.<sup>16</sup>

There is a tendency toward low serum albumin concentration, which seems to develop after the disease is manifest and to persist after the diagnostic evidences have disappeared. Serum protein determinations are of value in estimating the severity of pellagra and in furnishing one criterion of cure.<sup>17</sup>

Hematoporphyrin is not present in the blood serum.<sup>18</sup>

The alkali reserve of the blood is normal.<sup>10</sup> Diminution in serum electrolyte concentration appears to be of greater importance than disturbance of acid-base equilibrium.<sup>20</sup>

The cyanide detoxifying power remains unimpaired, provided the supply of cystine is adequate.<sup>21</sup>

The total amount of nitrogen in the urine is low.<sup>10</sup>

The ratio of urea is "low enough to suggest liver insufficiency."<sup>10</sup>

The uric acid excretion is low.

The creatinine coefficient (ratio of excretion to body weight) is much below normal and remains low during convalescence. It is low in proportion to the severity of the disease as manifested clinically.<sup>10</sup>

Small amounts of creatine are eliminated in the urine.<sup>22</sup>

The excretion of thiocyanate is low as compared with the content of the urine at the time of discharge of the patient as being cured, but the increase during convalescence is not proportional to the increase in the total content of nitrogen.<sup>12</sup>

Voegtlin<sup>23</sup> found the amounts of ethereal sulphates, neutral sulphur, hippuric acid (Murlin, 1920) and indican increased. He regarded the purin metabolism as being normal.

Acetone and diacetic acid are not found.<sup>24</sup>

After a curative diet, the products of exogenous metabolism rise to approximately normal.<sup>10</sup>

Human milk does not show chemical changes that are considered to account for the disease in nursing infants.<sup>23</sup>

In five cases of uncomplicated pellagra, as compared with normal controls, extensive chemical analyses of the central nervous system revealed the following principal abnormalities:<sup>25</sup>

The water tended to increase, there was loss of lipoids, and the proteins tended to decrease slightly.

There was a decrease in the cerebroside, phosphatides and sulphatides, which is probably due to an increased lipolytic process associated with the degeneration of the tissues.

There was a relative increase in the cholesterol content of the cerebellum and spinal cord.

The cholesterol in the cerebrum was diminished.

The proteins seemed to be the least affected of all the constituents. They were present in normal amounts in the cerebrum and cerebellum. In the spinal cord, a decided increase was noted in the dry tissue, whereas in the fresh tissue the proteins were decreased.

There was considerable increase in extractives, which compensated for the loss of lipoids; the nitrogen-containing, noncolloidal extractives were especially responsible for the increase in extractives.

There was a loss of neutral sulphur in the cerebrum and spinal cord and an increase in this constituent in the cerebellum, "which may possibly be interpreted as a disturbance of the oxidative power of the colloidal sulphur compounds."

### Discussion of Etiology:

It would seem to the writer that the dietary deficiency theory of the disease is basically sound, but that further progress in dealing with the disease depends on a recognition that the theory probably has a series of limitations. Susceptibility of the individual and environmental factors noted in the disease have dietary require evaluation. The following quotation

The exogenic Laboratory Bulletin No. 153<sup>26</sup> relative to seasonal urinary excretion illustrates both the emphasis put on the dietary theory

There is an emphasis and the scientific reserve characteristic of their work. low excretion of the disease brings out concretely what has long been recognized clinically, abnormal, and post pellagra 'normally' tend to get well in the fall with the

advent of cool weather. This old and very striking clinical observation gave rise to the idea that in some way the cooler temperature in itself had a beneficial effect. In reality, however, the decline in the season of prevalence, even allowing for the limitations of our data, sets in before the advent of cool weather, so that this can hardly be the real explanation of the phenomenon. The similarity of the curve of prevalence to that of incidence naturally suggests that the factors, or some of them, operating to limit the season of incidence also operate to cut short the attack.

"Of the factors suggested as probably concerned in cutting short the season of incidence the normal seasonal modification in food supply occurring in the summer would seem to be the only one that can reasonably be suggested as capable of operating in such a way as to limit the duration of the attack—that is, of prevalence. *A priori*, this factor would seem entirely adequate to explain the normally self-limiting character of the attack. But whether it actually operates in the manner here suggested, as seems to us most probable, or whether some other factor or factors alone or in coöperation with the seasonal modification in diet are concerned in the explanation of the phenomenon under consideration remains for further study to determine."

The discussion of the age and sex incidence of pellagra given by these authors is similar in its emphasis on the economic factor. It assumes a system of distribution at the family table that results in a survival of the economically fittest within the domestic circle. One may hope that a physiological explanation can be substituted.

To the writer it would seem that among the subjects that would justify further investigation in relation to pellagra are heredity, geographic and seasonal variations in rate of tissue oxidation, the physiology of creatinine and creatine, sulphur intake and metabolism, and the influence of solar radiation.<sup>27</sup> The hereditary tendencies displayed by goiter make it not unreasonable to investigate further the possibility of a similar tendency in pellagra. A seasonal decline in the normal rate of oxygen consumption in areas where pellagra is endemic has been observed, corresponding with the seasonal rise in the incidence of pellagra. Physiological creatinuria and pellagra incidence reveal a rather striking parallel with regard to age and sex.

Data have been presented which were thought to suggest that a deficiency of sulphur in the diet, errors of sulphur metabolism in the disease, and solar radiation, are important. These ideas were grouped in the following conclusions.

That there are biologic effects due to radiant energy is not open to question, and that some of these are related to pellagra seems probable.

An adequate supply and a normal metabolism of sulphur appear to exert a protective influence against the pathologic effects of solar irradiation. The evi-

dence suggests that an inadequate supply of sulphur as cystine is an important cause of pellagra, and that the abnormal metabolism of sulphur is an important feature of pellagra.

The distribution of pellagra and the variations in its prevalence and incidence suggest that solar irradiation, under certain abnormal conditions of nutrition, is an important factor in the etiology of pellagra, and that the reaction to solar rays not only is conditioned by the nutritive state, but depends on a state of the tissues determined by contrasts in degree and intensity of exposure during the annual cycle.

The more important considerations on which these suggestions are based are here briefly summarized.

A possible relation of a deficiency in supply or utilization of the sulphur-containing amino-acid cystine to the etiology and pathology of pellagra is more probable if it is assumed that solar radiation is also a factor in the etiology of pellagra. The role of the latter has often been suggested by clinicians, as Enright<sup>3</sup> in Egypt, Cluver<sup>28</sup> in South Africa, and various American authors.

Sulphur in the form of cystine appears to exert a protective action against exposure to solar radiation in low forms of animal life. Its high concentration in epidermal tissues of higher forms of animal life suggests a possible protective action in these animals also.

There is evidence to suggest that an abnormal state of the lens of the eye with reference to the normal reversible cystine $\rightleftharpoons$ cysteine reaction, together with exposure to ultraviolet wavelengths of light, is important in the pathology of cataract. This may serve as an illustration by analogy of the role of sulphur and light in pellagra. Langston and Day<sup>29</sup> have consistently produced cataract in white and gray rats on vitamin G deficient diets.

Eckstein said that the disturbed metabolism of rats on a vitamin-free diet is unable to stand the additional strain put upon it by irradiation. This appears to be illustrated in the experiments carried out by Koch and Voegtlin<sup>25</sup> by feeding a restricted vegetable diet to monkeys. Their tables clearly show the extent of exposure to sunlight and appear to warrant the notation of an inverse correlation between the hours of exposure and the duration of life, and a critical influence of short exposures following dietary restriction and previous exposure to sunlight.

Cystine, protective against ultraviolet radiation, promotes the growth of vitamin G-containing yeast. Its role is related to oxidative

processes and to the detoxification of cyanogen compounds, both of which functions are disturbed in pellagra. It is necessary to the growth and maintenance of animals, and, as shown by Lightbody and Lewis,<sup>30</sup> is specifically necessary to the normal development of hair in the rat. It is important in the nuclear activity of cell division,<sup>31, 32</sup> and, as Ropshaw<sup>33</sup> has shown, both light and the cysteine-cystine reaction play a role in pigment formation. Glutathione (cysteine in combination with glycine and glutamic acid) was originally isolated by Hopkins from yeast and from muscle and liver, all rich in vitamin G. The occurrence of cystine has been remarked in the foods that Goldberger and his associates advocate as preventive of pellagra, and in general they contain cystine (or sulphur) in proportions comparable to the value assigned by Goldberger in the prevention of pellagra. Abnormalities of sulphur metabolism in pellagra have been referred to above. The evidence is suggestive that a lack of cystine may have a specific relation to the etiology of pellagra and that abnormal metabolism of sulphur may be an important feature of pellagra.

**Epidemiological:** The geographic distribution of pellagra is limited rather closely to the isothermal line of 80° F. average July (in the northern hemisphere) temperature. The possibilities in the interpretation of this fact are, of course, wide. Actual measurements of seasonal variations in intensity of ultraviolet radiation at Davos, Switzerland conform quite closely to a curve representing the seasonal variation in air mass traversed by the solar rays at the corresponding latitude. The pellagra belt appears to be limited on the south by an adequate exposure throughout the winter to protect against the disease, and on the north by the fact that exposure in summer is rarely sufficient to produce the disease. These ideas are inherent in the familiar facts of sunburn.

The seasonal incidence of pellagra in southern United States, as reported, corresponds to the seasonal incidence as observed by house canvass. There is a marked tendency for the curve of incidence to rise and fall with the seasonally decreasing and increasing air mass through which the sun's rays filter. Or, if the curve of ultraviolet intensity at Davos is considered as applicable to the southern United States, the tendency is for the seasonal incidence of pellagra to rise and fall with increasing and decreasing intensity of

ultraviolet radiation. Reference has already been made to an explanation of this phenomenon based on the normal seasonal modification in food supplies. However, it is further noted that a secondary rise or peak of incidence of pellagra following the summer solstice is not seen in the data studied save when there is a corresponding excess of sunshine due to absence of cloudiness. In general, the curve for pellagra deviates from that for the air filter to correspond with a curve of excess sunshine, when it deviates significantly at all. Doubtless in August as many persons have a tissue metabolism favorable to the development of pellagra as in either July or September, but lack whatever influence there may be in a relatively greater solar radiation. The decline of the season of prevalence and of incidence does set in before the advent of cool weather, but it does not set in before the advent of a decline of the sun toward the south.

A study of economic factors in cotton culture, including acreage, yield and price to the farmer, compared with pellagra incidence, seemed to show significant correlations. But the correlation appeared to be closer if both the climatic factor and the recent previous incidence of pellagra were taken into account along with the economic factor.

With reference to the unsatisfactory status of the seasonal modification in food supply as a full explanation of the seasonal variations in pellagra incidence and prevalence, it is interesting to note that both Leader and Thatcher, Sure and Walker found a seasonal variation in experimental rats fed, under controlled conditions, a diet deficient in vitamin "B complex."<sup>2</sup> This result, obviously, was remote from the influence of seasonal modification in available food supply. Boggs and Padget<sup>3</sup> classified their cases into simple pellagra, pellagra associated with alcoholism and pellagra complicating another disease. They noted in each the same seasonal variation as to month of onset. It is difficult to apply the idea of a seasonal modification in food supply to the last two classes.

Another interesting feature of Boggs and Padget's report is the superior results they obtained by liver feeding as compared with their other methods of treatment. It would carry the discussion too far afield to consider the clinical similarities between pellagra and pernicious anemia and the recent suggestion of Strauss and Castle<sup>34</sup>

that the lacking extrinsic factor in the etiology of pernicious anemia is vitamin B<sub>2</sub>.

It does, however, pertain more closely to the subject at hand to mention the report of Sabry,<sup>35</sup> in Egypt, with reference to the treatment of pellagra by intravenous injection of sodium thiosulphate. The results in twenty-four cases were considered to be good. The question has been raised as to whether the results were attributable to the diet used rather than to the sodium thiosulphate. However this may be, the writer, while he has had only a negligible experience with the method, has noted that, after failure to gain satisfactory improvement under dietary treatment faithfully followed for six weeks, the intravenous use of sodium thiosulphate gave good results. In another case the condition of the tongue, gums and buccal mucous membranes made desperate the problem of any feeding and the condition of the patient rendered doubtful the results of any treatment. The response to the first injection of sodium thiosulphate was, in forty-eight hours, an improvement of the mucous membrane lesions so as to permit the beginning of suitable feeding, and continuation of the injections apparently resulted in unusually prompt recovery of mouth and skin lesions along with improvement in the general condition. Both of these cases were associated with alcoholism.

#### TREATMENT

With regard to the treatment of pellagra, the most obvious need is prevention. As stated in the beginning of this article, it would appear that the endemic disease can be prevented if the measure advocated by the United States Public Health Service can be made effective, namely, the inclusion in the diet of adequate amounts of vitamin G. This is a public health problem in its broadest sense. It would seem to call for an educational program to be carried on by a variety of agencies. But beyond this, since the remedy lies in the field of applied economies, it is a problem for doctors of economy. This is hardly an appropriate place, nor is the writer competent, to discuss this side of the question. But it may well be that improved agricultural conditions will actually increase the incidence of pellagra if tendencies to a single crop economy are intensified by increased values of staple crops that are neither food for man nor feed for animals. The writer ventures only a single suggestion as to the



educational program in behalf of diversified crops. The sources of credit which supply the tenant farmer and the mill worker are few in number and of a high grade of intelligence as compared with their debtors. These creditors are in position to influence the purchases and the planting of their customers and "croppers" with pellagra-preventing effect. To do so would require no transformation of the business man's instincts, humane or practical. The creditor may be taught to fear pellagra in his debtor.<sup>36</sup>

In the curative treatment of pellagra, the basic principle for the present, at least, is the supply of adequate amounts of vitamin G. The more important sources of this vitamin as ascertained to date have been listed above. The exceptional value of yeast as a source of vitamin G makes it an important addition to the dietary regime. Liver, also, has been shown to be unusually rich in this factor, and the literature contains evidence of improved results when liver or liver extract is used.

Occasionally, nasal feeding with a tube passed to the stomach has served to initiate the changes necessary to adequate feeding by the oral route.

Symptomatic treatment will not be referred to, except in connection with the achlorhydria or depressed acidity usually present. This is generally conceded to call for the administration of dilute hydrochloric acid. At times, however, the condition of the mucous membranes of the mouth makes its administration impracticable for the time being, and there has not been observed any report of a specific effect. The most conspicuous indication for its use is diarrhea.

The mental condition of the patient may require observation and restraint in order to avoid harm to the patient or others.

Various writers have emphasized the importance of guarding against exposure to light both during the stage of active lesions and, lest recurrence of symptoms be induced, too early in convalescence.

The reported use of sodium thiosulphate is too meager to establish a value for this remedy. It does, however, seem to the writer that it merits further trial.

When the symptoms of pellagra have been brought under control, the liability to recurrence appears to be sufficiently offset by a balanced diet containing sufficient vitamin G.

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# PLANNING TREATMENT FOR OVERNOURISHED AND UNDERNOURISHED PATIENTS

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Not many years ago the struggle for existence was so severe that a rotund figure was an evidence of health and prosperity, a spare one a social and business handicap. The sentiment of this tradition possibly accounted for the popularity, a generation past, of a state of overnutrition acquired with enthusiasm during the years of middle age. The present era of machine-produced plenty when not only the worthy, but most of the more slovenly, can get not only enough but too much to eat, has changed this attitude. It is emphasized, too, by life-expectancy tables of insurance companies which show the menace to life and continued good health, with advancing years, of abnormal nutritional states. At present appreciable grades of obesity are considered a misfortune and a state of emaciation, by many, a praiseworthy accomplishment. Because of these points of view physicians are seeing more patients with no disorders other than variations from normal weight. The obese beg for relief from the embarrassment and distress of their excess weight, hoping it can be done without effort. The emaciated patients, proud of their figures, complain of a number of symptoms arising, unsuspected by them, from their state of undernutrition. Enthusiastic cooperation of the patient is essential in the treatment of these disorders if satisfactory results are to be obtained. Cooperation of the patient is enlisted best by a detailed statement of the conditions so that the facts are faced frankly at the beginning.

## OVERNUTRITION

There is confusion in the minds of most patients and of some physicians as to the nature and genesis of obesity. Weight producing substances cannot be absorbed through the skin or inhaled. They must be swallowed. Except in those easily recognized disorders associated with water storage, weight increase results only from in-

gested food. Regardless, therefore, of any other consideration, inquiries as to why a patient has become fat and remained so are inquiries why he has eaten too much and continued to do so.

Obese patients often say that if they eat any less than they do, to say nothing of the rigidly restricted menu which they must follow to lose weight rapidly, they feel weak and spiritless. This idea suggests the presence of some metabolic anomaly whereby the essential active body tissues are starved while the ingested foodstuffs are deposited as fat. No such condition has ever been shown. Evidence against such a metabolic disorder is afforded by a series of over two hundred patients successfully reduced with diets in which all the essential foodstuffs for vital tissues were given in menus containing not over six hundred calories. These patients were not weakened or debilitated but showed improved spiritual and physical vigor. This resulted because the vital tissues were not being wasted. Special studies on a large number of these patients showed that they remained in nitrogen equilibrium and their creatinin coefficients for ideal weight remained constant.<sup>1</sup> These patients were using all the ingested food for the active functioning tissues. With a food intake of such low caloric value, if any had been diverted for the deposition of fat, it would have resulted in debility, and in addition the patients would have been in negative nitrogen balance and the creatinin coefficient would not have remained constant. This series of patients included men and women from age twelve to sixty-eight, from several different nationalities and races, and some who could have been called pituitary obesity and other endocrine types. The most common evidence of endocrine disorder was disturbance of menstruation. Except where demonstrable organic disease was present in the generative organs, the menstrual disorders were improved in every case and apparently completely relieved in a few by correction of the excess weight by diet alone. Such observations do not eliminate the possibility of some obscure metabolic anomaly or endocrine disorder whereby fat is deposited at the expense of vital tissues if an excess amount of food is not eaten, but the positive proof that none was observed in a series of patients of this length and diversity suggests that it does not exist. It is possible some primary metabolic or endocrine disorder may be present but if so it is not one which has been recognized or which has as yet afforded a practical suggestion

for treatment. Obesity cannot be corrected except by creating a difference between energy output and energy intake.

One theoretical possibility in the correction of obesity is to increase the energy output to balance the increased energy intake. Two methods are available: more exercise and thyroid medication.

More exercise in obese patients is impractical, because an amount necessary to result in appreciable reduction would be so distasteful that the patients would not do it. Point is given to this by dwelling upon the amount of increased physical work which all physicians know can be done without weight change by increasing a normal intake of 2500 calories to 3300 calories; and that these calories are contained in a little more than three ounces of butter. Even though willing to exercise vigorously, the necessary amount would be unwise for most obese patients. The excess weight has already thrown a burden of menacing proportions on the cardiovascular and renal systems, the arches, knees, and lumbosacral joints and regional muscles which should not be increased. On the other hand, exercise in patients who are so young and sturdy that it is not a menace, results in increased appetite which often defeats its purpose.

Thyroid administration as a way of increasing energy output in obese patients is impractical because unwise. In these patients the caloric exchange is already higher than normal for them if of ideal weight. A woman who weighed 370 pounds showed an oxygen exchange of 99.0 calories per hour, giving a basal metabolic rate when calculated in the ordinary way of plus 8 per cent. This caloric exchange calculated for her active functioning tissue as measured by ideal weight gives a rate of plus 67 per cent. One would not consider giving a patient of normal weight and a basal metabolism of plus 67 per cent. a higher rate of oxygen exchange by thyroid medication. It is similarly contraindicated in obese patients in whom there is already this physiological strain which should not be increased.

Excess weight associated with diminished function of the thyroid gland does, of course, indicate thyroid medication. Thyroid is prescribed for the myxoedematous state, and only in such quantities as will bring the basal metabolic rate up to normal for ideal weight. In such quantities some weight reduction will result, to a large extent by the elimination of stored water. If a greater reduction in weight

than results from this dosage of thyroid is desired, limitation of energy intake by reduction of diet is essential. If the thyroid medication is pushed to produce a metabolic level higher than that normal for the active functioning tissue of the patient, the damaging results of the physiological strain thus induced and the attendant distressing symptoms ensue just as they do in patients where the excess weight is due to fat tissue alone. It should be observed that myxoedema as a cause of excess weight is very rare, not more than 1 or 2 per cent. of patients presenting themselves for weight reduction.

Other glandular products have been suggested in the treatment of obesity. Antuitrin is perhaps the one most used recently. Glandular products are not given in the hope of impairing the appetite and thus diminishing energy intake. Nor has it been shown that they increase energy output as thyroid does. The hope in their use lies in the correction of some as yet unknown metabolic anomaly, the very existence of which may be seriously questioned, or possibly as a tonic stimulating to a more active life, more enthusiasm. Unfortunately a corresponding or even more than proportional increase in appetite is to be expected just as reasonably with any correction of a debilitated state which may result. Furthermore, any appearance of debility associated with obesity can be attributed in many instances to the physiological strain of the obesity itself.

Energy output varies normally with different individuals and in the same individual at different times. But, however low the energy output from whatever cause it is possible to reduce wholesomely the energy intake below it. All the known foodstuffs essential for maintaining health and vigor can be included in food yielding fewer calories than are necessary to maintain normal weights to say nothing of maintaining or adding to excess weight. An adequate amount of protein for nitrogen equilibrium, sufficient carbohydrate to maintain a safe ketogenic-antiketogenic ratio under any circumstance, all the needed inorganic salts and known vitamins can be included in an intake of less than 700 calories.

Weakness and debility result only if the removal of essential foodstuffs accompanies a reduction of the total caloric intake. Practically all diets originating in gymnasiums and beauty parlors commit this fundamental error. In view of the considerations presented above, a properly planned menu should not cause difficulty, and prac-

tically it does not as shown by the series of patients treated in this manner.

It is important to convince the patient that the material which goes to make his excess weight can enter by no portal except his mouth; that that material is food only; that essential foodstuffs are not diverted from the depots where they are needed for the formation of useless fat; that his weight cannot be reduced safely by balancing his excess of food intake by increased energy output in the form of added exercise or by drugs. Convinced of these facts, the patient realizes that he is too fat only because he eats too much; that to reduce he must eat less; and that there is a menu for him that will reduce him safely and with relative rapidity. Those patients who do not face these facts frankly before beginning to diet do not obtain satisfying results; those who do, almost invariably succeed. Having decided to give up the fun of eating for the limited period necessary, they fear that they must give up their initial hope of being relieved without effort of the annoyance and menace of their excess weight. In this they are agreeably surprised.

Appetite is an intangible component but probably its character, given a sound digestion, results originally from acquired habit. Practically all obese patients will say that they do not eat very much. Careful investigation of this statement has in every instance proved it, as of course it must, to be incorrect. When the habit of eating too much is established the amount of food necessary to give a feeling of satiety constantly increases. This probably results from an increased capacity of the stomach to hold food comfortably, and from a smaller proportional rise above the basal calories of the specific dynamic reaction of the food ingested. With the limitation of food intake the capacity of the stomach to hold food becomes less. At the same time the level of basal calories falls, so that as related to this lower level the proportional rise of the specific dynamic action of the food ingested is greater.<sup>2</sup> Probably for these two reasons a much smaller amount of food gives an equal feeling of satiety. This adjustment takes place within several weeks, but even before that, even after the first few days of dieting, four out of five patients are not hungry. They become bored with the limited menu, but are comfortable. The occasional patient who continues to complain of hunger confuses this sensation with the "memory of the fun of eat-



ing." He will usually admit this error of interpretation when the differentiation between the two sensations is pointed out. There are patients in whom sensual indulgences form so great a part of their enjoyment of life—in the case of the obese it is eating—that life is uninteresting without them. These patients elect to continue their gustatory sensualism. They will not diet. They cannot be reduced by other means. They are doomed to lifelong obesity.

The diets which are given eliminate all calories except those carried by essential foodstuffs. They afford one gram of protein per kilogram of ideal weight, approximately two-thirds as many grams of carbohydrate, largely in the form of 5 per cent. vegetables, and other foods necessary to fortify the vitamin and inorganic salt content. Care is taken to include the minimum amount of fat possible while giving an adequate amount of protein.

The menus below are illustrative of those which have been used with success in patients whose ideal weights were 55 and 70 kilograms respectively.

*Diet for Patient—Ideal Weight—55 Kilograms*

C—40	G	= 73	
P—55	Ratio	= .45	
F—low	Calories	= 461	Bulletin #28

Food	Grams	Carbo.	Protein	Fat
Egg white.....	80	..	10	..
Orange.....	100	12	1	..
Egg.....	50	..	7	5
Peas.....	35	6	2	..
Round steak.....	140	..	32	4
Radishes.....	50	3	1	..
Lettuce.....	80	2	1	..
Celery.....	30	1	..	..
Peaches.....	80	8	..	..
Raspberries.....	60	8	1	..
		40	55	9

Breakfast		Lunch		Dinner	
Orange.....	100 Gm.	Round steak.....	70 Gm.	Round steak.....	70 Gm.
Egg.....	50 "	Fresh pens.....	35 "	Radishes.....	50 "
Egg white.....	20 "	Lettuce.....	40 "	Lettuce.....	40 "
Brewer's yeast.....	3 "	Celery.....	30 "	Raspberries.....	60 "

plus water.....	40 "	Egg white (hard		1 B&W Alkaline	
1 B&W Alkaline		cooked).....	60 "	Tablet o water....	200 "
Tablet o water....	200 "	Peaches.....	80 "	Viosterol.....	mvi
Viosterol.....	mvi	1 B&W Alkaline		Tea.....	150 "
Tea.....	150 "	Tablet o water....	200 "		
		Viosterol.....	mvi		
		Tea.....	150 "		

*Diet for Patient—Ideal Weight—70 Kilograms*

C—40	G	= 82
P—70	Ratio	= .48
F—low	Calories	= 521

Bulletin #28

Food	Grams	Carbo.	Protein	Fat
Milk.....	150	8	5	6
Gelatin.....	10	..	9	..
Egg white.....	65	..	8	..
Pineapple.....	90	9	..	..
Orange.....	50	6	..	..
Brussels Sprouts.....	100	3	2	..
Haddock.....	100	..	17	..
Round Steak.....	120	..	27	3
Carrots.....	80	7	1	..
Raspberries.....	55	7	1	..
		—	—	—
		40	70	9

Breakfast	Lunch	Dinner
Orange..... 50 Gm.	Haddock..... 100 Gm.	Round steak—ground 120 Gm.
Milk..... 150 "	Brussels sprouts.... 100 "	Egg white..... 65 "
1 B&W Alkaline	Pineapple..... 90 "	Raspberry Juice... 55 "
Tablet & Water.. 200 "	Gelatin..... 5 "	Gelatin..... 5 "
Brewer's Yeast plus 3	Water..... 100 "	Water..... 100 "
Water..... 40 "	1 B&W Alkaline	Carrots..... 80 "
Viosterol..... mvi	Tablet & Water.. 200 "	1 B&W Alkaline
Coffee..... 150 "	Viosterol..... mvi	Tablet o water... 200 "
	Tea..... 150 "	Viosterol..... mvi
		Tea..... 150 "

It is possible to compile menus somewhat more inviting, certainly more bulky. This has been found to be an unwise practice. Patients who will not be happy with a menu of limited bulk will not continue with one of greater bulk. The smaller the diet possible, the less appetite there appears to be. Not infrequently patients enquire why they are not hungry with this menu when with less severe limitation of caloric intake to 1200 or 1400 on previous attempts to reduce, they have been hungry all the time. Furthermore, this gustatory discipline reforms, for most patients, the abnormal appetite which

has resulted in their having become obese so that when reduced they can maintain their corrected weight without apparent self-denial. This most desirable result does not follow when the calories are not so strictly limited or, when with the minimum calorie diet mentioned above, artificial bulk is added or sensuality in appetite is indulged.

It may be said in regard to obesity:

1. Obesity results only from swallowing an excess amount of food.
2. Obesity can be relieved safely only by limiting the amount of food eaten.
3. Diets for the reduction of obese patients need contain no more calories than are inseparable from the essential foodstuffs, never more than 700 calories.
4. Obese patients are more comfortable on these limited menus than on more generous ones, provided they frankly face the facts and resolve at the beginning to give up "the fun of eating" for a period.
5. The patients who do not accept this point of view almost invariably fail. They probably are personality types in which sensual delights form so great a part of their enjoyment that life is not worthwhile without such indulgence.

#### UNDERNUTRITION

In contradistinction to obesity, undernutrition is often associated with disease, the relief of which automatically permits the attainment of normal weight. In addition to these cases there are undernourished patients with no demonstrable disorders which require correction. A few of this large group are thin because of consciously limited intake. There is no convincing evidence that unexplained endocrine dyscrasias, central nervous system disorders, or metabolic abnormalities afford specific causation for the remaining patients of the undernourished group. Critical examination of the available facts make it seem more plausible that a faulty appetite results from a chronic debility, itself in turn originally caused, or kept operative by, inadequate food intake. Relief of these patients demands breaking into this vicious circle by correction of the faulty food intake. Whether secondary to some demonstrable disorder or to a deficient appetite, undernutrition results, as obesity, from a discrepancy between energy intake and energy output, and can be corrected by no

measure except correcting this relationship. The patient who has become emaciated during the course of acute illness regains weight after recovery with relatively little or no effort because of improved appetite and low energy output in convalescence. The patient undernourished from no demonstrable cause except the insufficient food intake of poor appetite increases the intake only with the exercise of firm purpose more exacting than that necessary for the control of the appetite in the obese. Everyone knows the acute discomfort of an overfilled stomach. Almost any normal meal in the undernourished will overload a stomach so long unaccustomed to receiving and handling adequate amounts of nourishment. The sharp and proportionally greater rise of the oxygen exchange in reaction to the ingested meal, as related to the low basal level of caloric exchange in the undernourished, is another factor contributing to distress.

Prompt physiological adjustments in heat regulating mechanism, cardiovascular activity, and no doubt physicochemical balances not suspected are instituted which produce discomfort. It should be emphasized that attainment of normal weight demands more, in effort and determination, of the thin patient, except those convalescing from an acute illness, than of the obese one. Again, as in obesity, the relief of this disorder demands the enthusiastic cooperation of the patient. This is obtained by convincing him that many symptoms arise from, or at least can be relieved by, correction of the abnormal nutritional state; and that this can be accomplished only by eating more.

The symptoms caused by or associated with uncomplicated undernutrition, as shown by a diagnostic survey and the relief resulting from correction alone, are diverse and often severe. In the psychic sphere they are those of general debility, inefficiency and lack of self-confidence, emotional instability, irritability, restlessness and inability to concentrate, insomnia. Blinding migrainous attacks, or minor headaches are relatively common. Weakness and easy fatigability are recorded in all case histories. The most frequent symptoms related to the cardiovascular system are tachycardia, premature beats, dizziness on sudden changes of position. A few patients complain of dyspnea. Gas on the stomach, symptoms of pylorospasm, and of spastic constipation are the gastro-intestinal references. An intermittent mucus diarrhea suggests mucus colitis as a primary

factor for the undernutrition in a few patients, but the result of subsequent treatment indicates that the reverse of this was the correct sequence. Painful and irregular menstruation are mentioned by some.

The correction of undernutrition by creating a positive caloric balance cannot be accomplished by decreasing the energy output alone. This is as ineffective in these patients as are efforts to increase the energy output of the obese. Strict limitation of activity of the most active patients does not result in sufficient economy of energy to allow storage at an appreciable rate, and in many cases the lassitude of general debility has already cut down energy expenditure to its lowest limits. Limitation of activity, also, does nothing to correct the known, or suspected, specific deficiencies of essential foodstuffs from which certain undernourished people suffer.

The general systemic disorders in even the uncomplicated cases of undernutrition suggest some obscure endocrine disorder and invite the use of endocrine products. Despite the fact that there is no lowering of the sugar tolerance or other evidence of disturbance of carbohydrate metabolism, insulin has been used by some. Possibly it stimulates the appetite. No specific beneficent effect is to be expected. The disorders of menstruation, chlorotic types of clinical pictures, and emotional instabilities have led to the use of various preparations of ovarian hormones. These alone are not effective in treating undernutrition.

The case for administration of thyroid is more interesting. A depression of the metabolism in acute starvation has been shown by Benedict<sup>3</sup> and others, and the lowered level of basal oxygen exchange in appreciable grades of undernutrition noted by Magnus-Levy in 1906<sup>4</sup> has been frequently confirmed since. DuBois<sup>4</sup> and others found little change in basal metabolic rate in moderate grades of undernutrition. An understanding of the mechanism of the depression of basal metabolism in the more acute and pronounced cases is of importance in deciding for or against the use of thyroid in these cases. This mechanism is uncertain. Deuel, Sandiford, Sandiford and Boothby<sup>5</sup> and others suggested that a drop in basal calories is related to the change in quantity of deposit protein. A series of undernourished subjects reported by Benedict showed a drop of 32 per cent. in the basal metabolism associated with a drop

of 6 per cent. of weight and only 3 per cent. of body nitrogen. Lusk<sup>6</sup> could not trace the lowering of the basal metabolism to diminished body protein or body mass. A primary hypothyroid state has not been shown in undernourished patients and it is altogether likely that the lowering of the basal metabolism is secondary to the low level of energy intake. When thyroid was given to one series of eighty-three patients by Berkman<sup>7</sup> many of them were reported to feel better and in most of these the symptomatic improvement accompanied an improved appetite. But additional food intake is also necessary and this alone results in the same general physical improvement. The possible contraindications to the use of thyroid are related to nitrogen metabolism. Undernourished patients are nitrogen-starved. There is not only deficient muscle mass as shown by the index of creatinin excretion, but also a diminution of the readily available store of deposit protein. With adequate intake the undernourished store nitrogen rapidly, putting on muscle mass as proved by the increased index of creatinin excretion, and adding to the deposit protein. It is reasonable to suppose that much of the improved vigor of the patients is related to this nitrogen storage and thyroid administration might be expected to influence this process adversely.

Almost all of these patients have low blood pressure and a small pulse pressure. Low blood pressure suggests cortical hormone as a possible adjunct. The case for cortin is still under investigation but in the few patients where it has been tried by the author, no benefits resulted.

Uncomplicated undernutrition is a deficiency disorder, but caused as far as present evidence goes, by deficiency of foodstuffs. The best evidence of this is the relief of symptoms to be obtained by an adequate food intake. One factor only, in addition to common sense, need be given consideration in planning the menu, and that is quantity. The capacity of the patient for the ingestion of bulk is the only limit to intake. Strang and Cox<sup>8</sup> studied sixteen patients who increased in weight from an average of 26 per cent. underweight to 10 per cent. underweight, an average of 5.9 kilograms in five weeks. They averaged 3320 calories per day intake. This was equivalent to 73 calories per kilogram of actual weight or 57 calories per kilogram of ideal weight. Subsequent analysis of the food taken

showed that protein supplied 7.7 per cent. of the calories, carbohydrate 27.5 per cent. and fat approximately 64 per cent. The daily intake averaged 3180 Gm., made up from general menus including all foodstuffs. The diversity of materials necessary to afford adequate calories automatically supplies the essential foodstuffs.

Patients who are thin without conscious limitation of food intake often say that they eat well and conclude that they do not utilize the food properly. This point was investigated by Strang and McCluggage<sup>9</sup> in nine of the patients mentioned in the preceding paragraph. For forty-one weeks of observation the feces averaged 8.3 per cent. of the weight of the food intake. The wider variations between total food weight and total weight of the stools depended upon the relative water content of each. The fecal solids averaged 31 Gm. and bore a strikingly close percentage ratio to the food solids ingested. The average stool contained 1.3 Gm. of nitrogen per day which was 12 per cent. of the food nitrogen. The ratio of fecal solids and nitrogen to food solids and nitrogen indicated that the patients had digested and absorbed 94 per cent. of the food intake. This efficiency of digestion was shown by patients who increased, suddenly, their daily caloric intake often by 50 per cent., as nearly as could be estimated from the uncertain figures available for their customary intake before beginning to diet. These observations do not indicate digestive inefficiency as a cause of the undernutrition and inspire one with confidence in forcing food intake in these patients in spite of discomfort.

All patients complain acutely of discomfort after starting the diet. It is noteworthy, however, that the complaints are general, not specific. It is a surprising fact that definite pain, gas on the stomach, nausea, dizziness, headache, or irregularity of the bowels are so rarely observed as to be unworthy of comment. The indefinite distress diminishes rapidly and soon disappears so that the patients eat more after the second week than during the first two. Small doses of tincture of belladonna and bromid seem to lessen the discomfort during this period. The appetite becomes normal in some. In many, however, it does not improve appreciably and the exercise of determination is necessary to eat sufficient food when so little satisfies.

A regular routine and much rest during the period of dieting

is absolutely essential. The regular routine is a physiological stimulus and a disciplinary measure. The increased amount of rest diminishes the energy output to some extent but is useful chiefly because it enables the patient to eat more with less discomfort. A necessary routine for these patients has been found to be nine hours in bed each night and one hour reclining in bed immediately after each meal. In this feature the treatment approximates the constant bed rest and enforced feeding in days past when splanchnoptosis was considered a primary etiological factor. These patients do not do as well with constant bed rest as with the short periods immediately after meals. It is important that the period of rest be limited strictly to the amount of time decided upon—usually one hour. If these patients are allowed to drowse through the afternoon, the stimulus of a strict discipline, and whatever appetite increase comes from that, and of outside interests is lost.

The aberration of appetite so important in both obesity and undernutrition is, in the latter, even more difficult to explain. Some undernourished are too fatigued, others do not exercise enough; some are constantly tempted with attractive dishes, others have suffered relative privation; some are care-worn, others indifferent and irresponsible. The undernourished further differ from the obese, many of whom can correct their abnormal appetite by a short period of discipline, in that their appetite is likely to continue to be abnormal for much longer periods. The ingestion of a sufficient food intake to maintain health and vigor demands from many of the undernourished continued effort. If they do not have a determined will to be well, they will relapse.

It may be said in regard to undernutrition:

1. Undernutrition resulting from an insufficient food intake in patients without demonstrable organic disease or metabolic disorders, is associated with many different and severe symptoms which are relieved by correction of the abnormal nutritional state.
2. Normal weight is attained by the undernourished only by ingestion of more food.
3. Undernourished patients show no evidence of inability to digest and absorb sufficient amounts of food to gain weight rapidly.



The amount may be as high as 75 calories per kilogram of actual weight.

4. The increased food intake causes general distress so that determination on the part of the patient is necessary.
5. The actual discomfort after starting diet becomes less after several weeks, but in most patients the appetite continues uncertain and maintenance of weight requires continued attention. Many of these patients, who do not have a determined will to be well, will relapse.

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# THE MENTAL ASPECT IN THE ETIOLOGY AND TREATMENT OF PULMONARY TUBERCULOSIS

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## INTRODUCTION

THE first exhibit in this paper that I would like to call to your attention is the writer. He well illustrates the mental aberration, temporary I hope, which sometimes occurs in patients with pulmonary tuberculosis, when they think themselves capable of performing tasks for which they are incompetent. I know nothing of psychology, nothing of psychiatry but, alas! much of the mental vagaries of tuberculous patients. As I have gone over the medical literature upon this subject I am led to suspect that I am not alone in my sad plight. Contradiction contradicts contradiction and the tuberculous patient is described as anything between an insane criminal and a saint too ethereal for this mundane sphere. You can pick your articles and take your choice of his character.

This conflict of opinion rests really upon communications such as I am now presenting. The sanatorium medical resident is busy caring for the physical disabilities of the patients under his care. The introduction of artificial pneumothorax and other forms of surgical treatment has added greatly to the demands upon his time. He is too rushed, too dog-tired at the end of his routine work to engage in psychiatric study of his patients. He is staggered when he reads that a psychiatric study of fifty tuberculous patients consumed 2,000 hours, about forty hours for each patient (Muhl). If this be true, then either a psychiatric specialist must be connected with the institution or else such studies cannot be made. Unfortunately many of us engaged in treating pulmonary tuberculosis are so impressed by the mental vagaries of some of our patients that we are led to comment upon them and without sufficient data to draw general conclusions based almost entirely upon the exceptional cases. These unwarranted conclusions are often copied from one article to another, from one book to another, and from constant reiteration are

finally accepted as true. The distorted mental reactions of the tuberculous are discussed not only in medical literature but they are emphasized and often dramatized in novels, plays, biographies and even in autobiographies. John Keats refers to his "unsteady and vagarish disposition." J. A. Symonds writes: "I wish and will not" and "It seems to be a phase of my disease that I should grow in youth and spiritual intensity inversely to my physical decay." We are all familiar with Dumas' "La Dame aux Camillias," Rostand's "L'Aiglon," O'Neill's "Last Straw" and "Bound East for Cardiff," and many works of fiction which describe the changed and changing mental attitude of the consumptive.

#### ETIOLOGY

I believe it is a generally accepted opinion that psychoses predispose to tuberculosis. The increased chance for exposure, the faulty dietary habits, the necessary confinement in some cases, the lowering of resistance to disease through mental conflicts, must all play some part in facilitating infection and in influencing the later development of clinical pulmonary tuberculosis. But that tuberculosis predisposes to psychoses in mentally sound patients is gravely questioned by many alienists. They do note, however, that tuberculosis like any other debilitating or shock-producing disease may bring to the surface certain underlying neuroses and psychoses, hitherto unsuspected defects in personality. What particularly interests us today is the question whether a neurosis can bring about the development of pulmonary tuberculosis and if it can, how often does it do so.

As regards the predisposing effect of psychic injury to tuberculosis most sanatorium records are of little value. Apparently physicians who have studied this problem feel that they play a very important part. Mental conflicts are not unusual in the tuberculous, and Pearson thinks more persons with such conflicts develop tuberculosis than do those without them. In fact he believes that an early diagnosis of the predisposing psychiatric state is of more importance than an early diagnosis of the tuberculosis, and, as we shall see later, in his opinion leads more often to recovery from both conditions and to a return to normal life. These psychic injuries are far from rare in the complex life of today. All of us see patients suffering from them and often we give them scant attention,

hoping that time alone will heal them. But unfortunately grave injury may happen before the *vis medicatrix naturae* has time to heal. The jilting of a lover, the loss of a dear one, intolerable conditions at home, social ostracism, moral conflicts, failure in business, all enter here. A man, the president of a nationally known corporation, was devoted to his wife who died after some months' illness of cancer. He never recovered from this loss and a short time thereafter he developed pulmonary tuberculousis. Other factors may have entered into the development of his tuberculousis but the idealization of his wife and the worship of her memory, without doubt played an important part. Similar instances occur frequently in the experience of all of us. The compensatory reaction to emotional trauma must not be overlooked for on the one side we see overwork in an effort to forget unpleasant experience and on the other side a shutting off or in of one's natural emotional reactions. The effect of this upon a harmless, latent, pulmonary tuberculosis may be to fan it into actual disease. Susceptibility to primary infection is common to all but the development of infection into clinical disease often depends as much upon psychological conditions, psychic injuries if you will, as upon definite physical conditions. Those who deny that pulmonary tuberculosis is ever the result of adult infection or reinfection must frequently trace the transition from simple infection into clinical disease to some such cause.

Through the vegetative or autonomic nervous system we maintain our existence. It controls metabolism and other processes necessary to life. Through it the emotions mediated by the brain express themselves. Their effect upon the glands, the heart and the movements of the alimentary tract are well recognized. To see that irritation of the sympathetic system does occur in tuberculosis, we have but to recall the unilateral dilatation of a pupil, and the unilateral flushing of a cheek early in the disease, the hectic flush later. Some claim that prolonged emotional conflicts may manifest themselves in certain functional disturbances which in turn may so reduce what we call resistance as to tend to change a simple infection with the tubercle bacillus into definite clinical disease. What these disturbances are and the details of their action are too theoretical to discuss. It has been noted (e.g. Ziegler and Levine) that some persons suffering from fear and other disturbing mental conditions with few or no

objective signs of disease may have even while resting an increased metabolic rate. So fear as well as hatred, shame, anger, become manifestly important because it has been clearly demonstrated that even though a patient is lying quietly in bed, seemingly at ease, he may not be resting at all on account of these disturbing emotional influences. Chronic tuberculosis, some would have us believe is a prolonged infection with the tubercle bacillus but that clinical manifestations result from changes brought about through these nervous influences. Anything that produces nerve exhaustion, says Silk, lowers the vitality of the individual and renders him susceptible to tuberculosis. At any given moment each individual has a limited amount of dischargeable nervous energy which is at the disposal of some form of stimulation (Sherrington). Fear and psychic trauma can drain the last drop of dischargeable nervous energy and therefore the greatest possible exhaustion may be produced. The fear experienced by an individual when he imagines he is suffering or is actually suffering, from some incurable and fatal disease produces a continuous drain upon the dischargeable energy and through the law of summation of stimuli produces nerve exhaustion rendering those not affected with the disease more susceptible to it and those actually suffering from the disease liable to a more rapid course and a fatal termination.

Mühl argues that since the great majority of people are at some time infected by the tubercle bacillus and yet only a comparatively few break down with a chronic form of tuberculosis in adult life, therefore, there must be some factor other than the tubercle bacillus responsible for failure of the body to defend itself against the disease. She apparently overlooks the possibility of the danger of frequently repeated infection. How submerged or apparent emotional conflicts can bring this about we have already mentioned. But when this author says that if children with incipient tuberculosis could be reeducated emotionally and have their energies directed along the right lines so that they would be free from repressed emotional conflicts there would be very little adult chronic tuberculosis, it seems to me that her conclusion is gratuitous. However after some thought upon the subject I am willing to admit that so-called psychic injuries can, and do, in a certain number of patients have some etiological bearing upon the development of latent into active pulmonary

tuberculosis. I regret that I know of no statistical study bearing upon this subject.

#### TREATMENT

However divided opinion may be about the etiologic importance of psychic damage in pulmonary tuberculosis the importance of psychological and psychiatric treatment in the disease is well recognized by all. Still it must not be forgotten that mental treatment only reinforces, never supersedes the physical treatment. That the mental aspect of many patients changes during the course of the disease and during its treatment is not strange. "Tuberculosis may produce," says Worden, "the following changes in the mental state of a patient: 1. a mental state accompanying tuberculous meningitis." This was well illustrated in the case of one of my patients, who became obsessed with the idea that he needed a colder climate during the summer than that of the Adirondacks. He headed for the North Pole and his family overtook him several hundred miles north of Quebec. "2. Delirious states which are found in the service cases due to the tuberculous poisoning." Fishberg thinks this state resembles that of a slight intoxication from alcohol. "3. In people with a structural defect in personality (meaning that they have developed habits which lead to mental disorders, moodiness, seclusiveness, suspiciousness, etc.), tuberculosis may liberate a true psychosis, such as: manic-depressive, dementia precox, psychoneurosis. 4. Tuberculosis may be complicated by other organic diseases such as arteriosclerosis, diabetes, etc. and the resultant mental state may be due to both diseases."

Every patient reacts mentally more or less to any disease from which he suffers and the longer the disease lasts the more noticeable usually is the reaction. "Emotions," Riggs states, "are primarily physiologic reactions and upon this fact are based the following conclusions of great importance to the practice of medicine: First, the disease, through disordered function must affect the emotions of the patient; second, emotions, in their turn, must through modification of function affect disease; third, treatment, likewise, must both affect and be affected by emotions." The patient, he says further, reacts to his disease (1) according to his instinctive and emotional makeup, (2) according to his intelligence, his power, potential or

acquired, to modify such reaction through understanding, (3) according to the degree of suggestibility he possesses specifically in regard to the given change. There are certain items common to all illness, pain, confinement, disability. Now confinement is an "aspect of illness which calls out specific responses from the sufferer. By restricting the mental horizon, by forcing the attention to focus on pain, discomfort or an abnormality of function, it produces at least a strong tendency to introspection. Of course, merely mechanical confinement of a previously active person is productive of discomfort both of body and mind, not to speak of the boredom of an active mind thrown out of its occupation. Inactivity also necessitates physiologic readjustments which add their quota of disagreeable sensations to those of the illness itself." Remember please that Riggs is here speaking of any chronic or long-lasting confining disease.

In the treatment of pulmonary tuberculosis a psychological problem confronts the physician as soon as he has made the diagnosis. Shall he tell the patient? I am convinced that in practically all instances it is wise to do so. At this time it is well to note how the patient receives the news, whether with shock, hopelessness, rebelliousness, calm realization or indifference. This reaction is modified by the type and severity of the symptoms, whether they occur slowly or suddenly, by the age of the patient, with its varying responsibilities and what is most important, by the previous personality of the patient. The previous personality, many think, determines largely the reaction to tuberculosis. It must not be overlooked that persons with slightly strange, possibly abnormal, mental traits are far from rare in the general population. The reaction of the patient may early indicate the best line of treatment and by following this line much time may later be saved. The loss of his position and of his income, the giving up of his house, the interference with professional plans, the breaking up of his home, the lack of support for those dependent upon him, all influence his attitude. "A man," says Banister, "with his principal sentiment organized around some ideal which is not egocentric is able to bear the disorganization caused by the disease and reorganize his life as may be necessary. The self centered man may lose his morale at once." However this may be from the time the diagnosis is made, in some cases even antedating this from the time a suspicion of the presence of the disease is .

aroused, influences may begin to affect the trend of the mentality of the patient. It is of interest and of help in the treatment of these conditions to endeavor to see exactly how patients do react. In a study of the histories of 1,499 patients, collected from various sanatoriums, Williams (L. R.) and Hill (A. M.) found that 59 per cent. were told the diagnosis immediately after it was made and 28 per cent. within a month. Thirty-three patients were not told for a year or longer. All these reacted as follows: not surprised, 12 per cent.; grateful, 26 per cent.; diagnosis accepted, 2 per cent.; ready to cooperate with the physician, 10 per cent.; unaffected, did not realize significance of occurrence or were philosophical, 20 per cent.; diagnosis doubted or disbelieved, 9 per cent.; disturbed to varying degrees, 18 per cent. This figure (18 per cent.) does not include all those who were more or less upset. About 4 per cent. reported that they went all to pieces, gave up hope, collapsed. Only in rare instances, they conclude, is it unwise to tell the patient.

The tubercle bacillus produces a poison which some have termed a toxin but if we accept the definition that a toxin is a substance capable of producing an autitoxin then the poison of the tubercle bacillus is not a toxin. However, it is a powerful poison and many effects are attributed to it. It is said to be the cause of most of the symptoms of pulmonary tuberculosis. Tuberculin is supposed to be one of its main components. It brings about destruction of the tissue through the allergic reaction. It brings about the formation of fibrosis, scar tissue, and so favors healing. It is supposed to have a peculiar affinity for nervous tissue and so is said to be the cause of the nervous and mental peculiarities so common during the course of the disease. Whether this poison can so seriously affect the normal central nervous system as to produce a psychosis is gravely questioned. Carncross studied 207 patients with pulmonary tuberculosis and thirty who did not have tuberculosis but thought at the time of study that they did have it. Both groups showed no difference in their mental reactions, which makes it improbable that the tuberculous poison had anything to do with the symptoms in either group. Dufour and Dide suggest that since cerebral symptoms may occur after the injection of tuberculin, this or a similar poison may be the cause of mental changes in the tuberculous. But it is pertinent to recall that an injection of salt solution can produce



the same symptoms. This suggests that the mental changes are not due to the tuberculous poison. The suggestion that the euphoria occurring in the afternoon may be due to elevation of temperature means only that it is possibly indirectly due to the tuberculous poison. The functional disturbances of the gastro-intestinal, circulatory and nervous systems, Boas (E. P.) thinks, are usually conditioned by a constitutional nervous instability of the patient rather than due to any specific manifestation of the tuberculosis.

The patient having been told the diagnosis naturally wants to know what he should do to recover. This brings up at once the question whether he should take treatment, the "cure," at home or in a sanatorium and also whether a change of climate is indicated. It is often impossible to decide whether or not home treatment is advisable until the situation in the home is fully known. The conditions there may be intolerable to the patient. Some observers would persuade us to regard the disease in some cases as a defense reaction to these conditions or as a mechanism of escape from them. For some the stress of life has been a burden from which it is a relief to escape. They lie down in the sanatorium with strange contentment. On the other hand certain traits of character may be revealed only in the home where the patient does not fear to unburden himself of causeless fears and worries. In an institution he may be led to overcome them by the many examples of restraint about him. Certainly, there he is forced to recognize that he is not the only sufferer that needs care and attention and thus egocentric habits and traits of selfishness may be curbed. The extrovert is permitted to tell his hard luck story but once or twice and so is forced to dwell upon more cheerful topics. This may react upon the introvert in an opposite manner and he may need encouragement to overcome slight psychic rebuffs or imaginary injuries. The retailer of gruesome stories to new patients is trying to compensate for his own fears. The patient who insists on discussing his own and others' symptoms is a nuisance and a danger. Here, of course, lies the weakness of the sanatorium, for mass treatment is in many institutions the only treatment possible. Individualization must be restricted to a few selected patients. Whether he be at home or in a sanatorium, the patient has long hours during which to brood over his hard luck and usually before long he has mental adjustments to make, for his disease

is generally painless and his attention is free to grapple with the many difficult problems that assail him. These, on account of his weakness, are hard to solve and may indeed grow harder as he grows weaker. Added to these uncertainties is always the fear that he may not get well. Fear is probably the one mental symptom common to all patients with pulmonary tuberculosis.

In tuberculosis conflicting factors, each probably of significance, play some part in the mental reaction. In the first place we are dealing with a chronic disease, known by the laity and the profession to be often fatal. During the last quarter of a century we have witnessed on this continent a vast propaganda to convince the public and even members of the medical profession that tuberculosis is a most curable disease. Whether or not it really is so concerns us less at the moment than does the admission of many workers that such propaganda was necessary to inspire an attack upon what had previously been considered an incurable and fatal disease. Many patients, among them even physicians, have never realized until stricken with the disease that their belief in the propaganda was insecure. It is one thing to face an acute fatal disease which lasts only a few weeks but an entirely different thing to live with a chronic disease having many fatal complications and often running a slowly downward course. The results of the disease are often seen by the patients on all sides for many of them are gathered together in sanatoriums early in the disease, later in special hospitals. Some deny that other chronic diseases, like nephritis, cardiac disease, disorders of the stomach, affect the patient in the same way that tuberculosis does. But until these patients in far advanced stages of the disease are brought together in large numbers and under circumstances where death is frequent and its advent known to the survivors, it is difficult to form a really accurate opinion of the effect of any chronic disease per se upon the mental state of the sufferer.

Now all persons well or sick dread death and in order to mitigate its fearful aspect beliefs have been developed concerning life after death. The American Indians have their Happy Hunting Grounds, the Buddhists have Nirvana, the Norsemen have Valhalla for the brave, the Greeks have the Elysian Fields, while the Christians consider death as a surcease of earthly woe and tribulation. All of these are, of course, a balm of resignation to the inevitable. In

tuberculosis the fear of death is acute, especially at first, and so the reaction to this fear is intense. For this reason the diagnosis of tuberculosis may bring to light an underlying and developing psychoneurosis but here an incorrect diagnosis would act similarly. Furthermore the effects of fear may not be manifested at once but appear some time later.

Fear, Eyre thinks, is a predominating emotion in the tuberculous; she found it in eighty-five of eighty-seven patients studied. Optimism, she regards as compensatory to an underlying dread of not recovering, a dread they resolutely refuse to admit to themselves or to others. The much discussed *spes phthisica* is absent at first and at this stage many arguments are necessary to convince some patients that they have any chance of recovery. Later, however, this attitude changes and then apparently hope overcomes fear. Not all experience this change; some want to hear only the cheerful things about themselves, others take their temperature only when they think it will be normal. They seldom frankly discuss their feelings, and when they finally realize their condition, familiarity tempered with bodily weakness often luckily removes many stings, for he who faces death constantly may come to face it fearlessly. "The fact that the progressive and terminal tuberculous patients are so apt to display the *spes phthisica* or unfounded euphoria," writes Bogen, "even though this may in fact be merely a defense reaction and that the convalescent patients and those whose disease is arrested or quiescent present so frequently a melancholic, complaining and pessimistic outlook leads to at least a suspicion that these mental states may, in fact, be due actually to the cause that they accompany and that the Pollyanna attitude of cheerfulness and contentment instead of being a positive therapeutic agent may in fact be a dangerous element in accelerating the decline of those in whom it is inculcated." McCarthy, working with patients in advanced stages of pulmonary tuberculosis at the Phipps Institute, found that 52 per cent. were depressed and gloomy. He notes that a patient may be very happy and yet hopeless about the outcome of his disease. Carncross found that 75 per cent. of the patients were hopeful and 29 per cent. depressed. A few minutes spent at the bedside of some fearful patient discussing the conquest of fear may do more to help him than a phrenicectomy.

Opinion differs regarding the value of the *spes phthisica*. As we have noted some think this form of over-compensation, occurring most frequently in the last stages of tuberculosis, is a danger to the patient and something to be guarded against but I believe that this "flight from reality," "this often pitiful attempt at self-deception," comes frequently at a time when it may prove to be a blessing. I am not sure but that the attitude in recent years has changed considerably and that today, when patients know so much about their own disease and about the various surgical attempts at treatment, the *spes phthisica* of former years is giving way to an attitude of mere resignation, accompanied by a bold front. It is not strange, therefore, that many patients in the sanatorium and elsewhere require the help of a skilled psychiatrist.

Worden has called attention to a mental attitude not uncommon among tuberculous patients and very important in treatment. The patient early experiences a conflict of ideas. What good will he be if he does get better? Will he fight the dread disease or end it all? In his quandary, he may seek refuge, as Worden says, in over-compensating for his fear by assuming a devil-may-care attitude towards the disease and its usual treatment. Aghast at his recklessness his family and friends attempt to frighten him with the fear he is attempting to escape. Apparently they influence him but little but later the memory of what has been said haunts him. If he continues to assume this false euphoric state due possibly in part to the disease, his friends redouble their terrifying prognostications. Rebuffed by relapses, weakened in body and in spirit, he becomes a suitable victim for a psychoneurosis. It strikes Worden as a great pity that such a valiant front against his disease cannot be turned into channels useful for the recovery of the patient. It should always be attempted.

Murray calls attention to the difference in attitude between patients in private institutions who are called upon to furnish their own funds and those in public institutions where they are under no expense. Many of the first group are anxious to return to work. As time for discharge grows near some of the latter group develop a fear, at times justified, that they will not be able to support themselves and their families. It is readily seen that this mental state would more likely be found in the earlier stages of tuberculosis for the advanced patients have little hope of such good fortune. This

fear may become so marked in some of these patients that they act like the shell-shocked patients of the war and in reality they are in the same condition.

Forster and Shepard at the Cragmor Sanatorium made a careful study of 100 patients with pulmonary tuberculosis, forty-seven men and fifty-three women. The average age was thirty-one, the range from eighteen to sixty-eight. The majority belonged to the upper strata of society. Of these, sixty-nine were found to be normal or became normal while under treatment in residence. Thirty-one presented an abnormal mental state in which the tuberculous patient allowed emotions such as fear, anxiety, fatigue, frustration, etc., to warp his personality so that he no longer thought or acted normally. Simple maladjustments during their residence were found in seven; psychoneuroses in twenty and psychoses or psychotic trends in four. The neuroses (nine, fatigue; ten, anxiety) were in no way peculiar to tuberculosis and were more frequent in minimal than in far advanced stages. The fatigue neurosis was more common in women, the anxiety more common in men; one half occurred in Jews. There was no correlation between the stage of the disease, the severity of the poisoning, sex or body types and the abnormal mental states which are common in tuberculosis, possibly more common than in other diseases. Tuberculosis, they conclude, is an emotional crisis and how a patient reacts depends upon his personality make-up before the onset of the disease. It is interesting to note what they say about body type for the slender body, the carnivorous type of Goldthwaite, is found more often in patients with dementia precox, among whom 50 per cent. are said to die from pulmonary tuberculosis. If there is such a thing as a "pre-precox" personality it would be easy to see how suspicion, seclusiveness, refusal of food might be more common traits in those with pulmonary tuberculosis and some neurosis. As a matter of fact two of these authors' four cases of psychoses were dementia precox.

Saxe would have us believe that early in tuberculosis the disease is accompanied by "neurasthenia, psychasthenia, and hysteria. As the disease progresses there is a more distinct change manifested by loss of will power and self control and the ascendancy of brute selfishness." Gerhardt states that the increased incidence of venereal disease in tuberculous patients (which however I have never seen)

is due to an abnormal increase in the sexual impulse. On the other hand Gubb states that the physiological influence of phthisis merely accentuates the natural predisposition to idealism. Much of this, of course, is all bosh.

The supposed change is disposition, noted in a number of patients, is probably due to the fact that the real character is now laid bare to vulgar gaze. The patient feels that he has his back to the wall and is fighting for his life. All sham and pretense are thrown to the wind and a potential selfishness fostered by the minutiae of treatment may come to the surface. This is often curbed in the sanatorium but at home the patient may try to exert despotic sway and often succeeds. Fortunately these reactions are rare. On the other hand some patients become apparently so transformed that their friends often weave about them a wreath of sanctity suggestive of another world. Patients reared in gentle families under the restraining influences of early training, education and vocation are not likely to show mental changes for the worse but reversion to childhood traits which disregard the difference between mine and thine occur even among these. The attitude of youth at school may be assumed and action based on the grounds that misdeeds undetected are not harmful. It is but natural that the emotions should be less restrained and unexplainable misunderstandings and differences arise. Jealousy is common and some patients cannot bear to have another receive any attention, even medicine, that is not proffered them. It is not unusual to have patients who continue to cough and spit tell those who have lost or are losing these symptoms that to lose them is a bad thing; obviously this is a defense reaction on their part. Please remember that although these peculiarities really exist still the majority of patients pursue the even tenor of their normal mental way. As a patient improves in health and regains his strength he usually approaches more closely to a normal mental state but this is not always the case. The prolonged cure, the many rebuffs, the prize all but within reach when slight relapse intervenes, shakes at times the morale of even the soundest. I have had a patient weighing over 200 pounds wake up at night and weep. I have seen many literally tremble, not at the fear of death but at the dread of again facing the uncertainty of recovery through months of anxiety. I have seen patients require months of psychic treatment after an

arrest of the disease before they would risk any exercise. Forced inactivity in some produces lack of concentration and even reading at times can no longer be followed. Indecision is striking and often patients like a physician to map out plans for them in great detail. The mental faculties do not always fail hand in hand with the failing strength and sometimes they seem even to become more acute. In other cases schemes plainly consigned to failure are gravely planned and they must then be begun at once. In one instance a patient attempted to corner all the cottages for rent in Saranac Lake and lost much money. Stevenson well describes such a patient: "Death catches him like an open pitfall and in mid career, laying out vast projects and planning monstrous foundations, flushed with hope and his mouth full of boastful language." Again let me insist that the vast majority of patients although possibly depressed at first soon rebound and whether they improve or fail remain the same men and women they were previously, optimistic or pessimistic, sanguine or choleric, sensitive or phlegmatic just as they were before tuberculosis came upon them.

For many years I have felt that nearly every patient with tuberculosis, especially with disease of long standing, is a neurasthenic. Also I have been convinced that many patients now diagnosed as having pulmonary tuberculosis, would formerly have been considered to have neurasthenia, particularly if they were young women. Perhaps these patients suffer from physical and mental insufficiency. In adolescence, says Munro, the symptoms may be attributed to laziness. Stevenson well describes the condition in "Ordered South." These symptoms usually occur at an early stage of the disease. As the infection progresses to the moderately advanced stage, when weakness often develops, will power and attention may wane. The optimistic may remain so, the pessimistic may grow worse. It is at this stage that artistic and literary characteristics may assert themselves. The tuberculous poison does not beget intelligence but intelligence, ambition, nervous tension, hard work, do open the way for tuberculosis. In the advanced stages of the disease we see naturally the most marked apparent change in the character of the patients. Strong infantile reactions may then come to the surface, there may be little repression concerning wants and trivial symptoms may be over emphasized. Some patients are, as Munro

says, hypersensitive for themselves, hyposensitive for others. Many refuse to think about their illness and live from day to day. I have felt that some cultivate this habit on account of the many disappointments they have suffered and that for them the "cure" may become a career. In the still more advanced stages patients often inquire how they are doing but seldom discuss their condition frankly or divulge their real feelings. If many of them did so then the tuberculosis specialists themselves would require psychiatric treatment.

Mühl studied twenty-five children with tuberculosis and found that eleven had an intelligence quotient of between 90 and 100, ten between 80 and 90, and four below 70. At this early age occurred many of the traits described as common in the adult patient with tuberculosis; suggestibility, irritability, depression, fear, anxiety, selfishness and "intensified type expression" (energy imbalance). The so-called pathological optimism is replaced in the child by depression. All had "horrid" nightmares and selfishness was common though attempts were made to conceal it. In both adult and childhood groups she noted in some a dual extrovert-introvert trend, which when exaggerated is responsible for a great misuse of energy; in one phase energy is expended in prodigious amounts, in the other it is aimlessly conserved so that little is used in the maintenance of a healthy adjustment. Has the tuberculous poison an extroverting influence? asks Turner, for some would have us believe that as the disease progresses some patients join the extrovert group. That changes in the mental outlook of the tuberculous patient often occur is not strange, that they do not occur more frequently is remarkable. Slight changes probably take place in most patients during a course of prolonged treatment but in the great majority they never go beyond the normal limits. Only a small number shows decided changes and very few indeed develop outspoken psychoses. From what has been said it is clear that not only the disease but also the treatment of the disease profoundly affects the mental state of many patients. The prolonged uncertainty over the outcome of the struggle they must make to keep their disease in a state of arrest, the inculcated fear of the effects of a wrong move, of a foolish weakness, or of the significance of a trace of blood, of a rise of temperature, may soon or late undermine a normally strong mind. Besides tuberculosis is a disease in which emotional strains are inevitably brought



about in family and in business relationships. Segregation emphasizes these and at the same time affords the patient leisure for brooding, which may easily cause undue distortion of his problems. In the weak and timid, who lack self-reliance and who incline to belittle the personal success which may justly stimulate self-esteem, a sense of inadequacy is always the first response.

From these considerations it is readily seen that mental quirks have a most important bearing upon the treatment of pulmonary tuberculosis and that all so afflicted need psychological help at some time. The modern treatment by prolonged enforced rest, followed often, as patients soon learn, by various surgical procedures, many of them fraught with danger, is not conducive to peace of mind. The refusal of many physicians to practice the art of suggestion, really a part of the art of medical practice, is regrettable. Dr. Trudeau was an adept at it. I remember well one of his patients, an exceedingly intelligent woman, who was relieved from a feeling of impending dissolution by capsules containing sugar of milk. Her husband warned me what her reaction might be should she discover the real nature of the very helpful drug which by the way, Pierce Bailey, who saw her in consultation, permitted her to continue. One day her nurse when piqued told her what the capsules contained. I saw her later when she informed me that she would not take any more of such medicine. Therefore, I gave her small doses of *cannabis indica*! Now if it is possible to soothe a troubled nervous system with a bottle of harmless pills, then I hold it to be my duty to prescribe them. The pills mean little to the physician but act as a sheet anchor to a worrying patient. It is an interesting fact that the majority of tuberculous patients at some period in their disease are very open to suggestion and he who knows best how to capitalize this great asset in the treatment of such a chronic disease helps his patients avoid many rough and thorny paths. The tuberculous patient has been by some supposed to be more susceptible than any other to suggestion. Possibly so, but from the number of cancer "cures" and "cures" for other diseases that I have from time to time seen advertised I am led to doubt it. The great number of consumption "cures" that formerly so frequently flooded this country reveal that the unscrupulous quacks have fully grasped this mental aspect of the tuberculous and have played upon it by means of

fraudulent advertisements. Christian Science and other faith "cures" may be helpful when they are not permitted to interfere with the proper treatment. In France I understand physicians order these things differently and wisely place reliance upon certain medicinal compounds, which are harmless and at the same time helpful, if in no other way than by suggestion. Renon approves of them and Kuss, world renowned for his work in tuberculosis, constantly employs drugs in this manner. A medicine to be used for this purpose should have a bright color, a definite taste, an engaging smell, and of course should be perfectly harmless though containing some ingredients like calcium and phosphorus, which may theoretically have some vague effect upon tuberculosis. Renon is said to have studied the effect of such "cures" and to have found that he could determine a "normal coefficient of amelioration" which was about the same for all of them. If the physician can believe in them, the drug is a vehicle of suggestion and more or less benefit follows. If he gives to the patient with enthusiasm some drug recently extolled by an enthusiast, benefit often follows. Harper of England recommended some years ago the use of urea for pulmonary tuberculosis and I recall one patient who always attributed her remarkable improvement to this waste substance! If in connection with a prescription the physician has a few minutes to spare during which to take up some of the psychic difficulties of the patient, using in connection with the preparation a little persuasion, far better results will often be obtained.

Some would place the rules, given to patients as a guide to exercise and general conduct while taking the cure, in the group of measures which act by suggestion. They replace, they say, the medicinal agents used for this purpose. I have no doubt that they lend themselves to aiding auto- and hetero-suggestion but pulmonary tuberculosis is a disease which demands heavy penalties when the fundamental laws of rest and exercise are broken. Formerly tuberculin was employed much more frequently than it is today and I am convinced that it acted partly by suggestion, although given with a cold, indifferent manner; for the little record books with minute notes concerning the result of each dose reacted strongly upon the patient and a slight overdose assured him that the tuberculin was not inert. If coupled with this some magic words were uttered

while the physician held poised the syringe just before injection, for instance "this is the life giving fluid," the patient was doubly impressed. Mathieu and Dobrovici at the Andral Hospital in Paris announced some years ago that they expected to receive in a few weeks a new "cure" for tuberculosis, "Antiphymose," with which only certain patients could be treated. At last the "cure" arrived and the patients were carefully selected, and new histories of them taken. The results upon the symptoms were striking and rapid; cough and expectoration decreased, the gain in weight varied from one to six and a half pounds. The "cure" consisted of the injection of salt solution! Faith in the physician is the most important ingredient of any "cure." Possibly today we have replaced the suggestive dose by the suggestive rule. Fishberg thinks that the Friedman turtle bacillus acted through similar channels of suggestion. The phrase "you are better again today," coming from the lips of a trusted physician is effectual psychotherapeutic treatment. Some believe that change of climate acts largely through suggestion, advancing to uphold the contention, that a patient may "wear out" a climate and need further change. That the stimulus of change is merely suggestion, I question, although I do live in a health resort. I cannot agree with Fishberg when he concludes that repeated attempts at artificial pneumothorax with failure to find the pleural space to which a few patients react very favorably, is due entirely to suggestion. The lung has been repeatedly punctured.

Malingering is probably no more common among patients with pulmonary tuberculosis than among those with other chronic disease. Applying the thermometer to the hot water bottle, burning the body with mustard to simulate a roentgen ray burn, simulating meningitis, the application by a nurse of lysol to the buttocks to simulate an injury from a bed pan in order to collect damages, have all been reported.

Some symptoms are very amenable to suggestion and a few minutes spent in explaining what cough is, what danger it entails and how easy it is to repress much of it, when unproductive, by relaxing the muscles and ceasing to try to raise all the mucus felt in the trachea, often does away with the need of a cough medicine. The same is true of insomnia. I have seen a patient go calmly to sleep after taking sugar of milk in a blue capsule who without it

laid awake all night. Suggestion morning and night with advice about muscular relaxation may do away with a long-continued use of hypnotics. The marked nervousness associated with intestinal tuberculosis, however, emphasizes the importance of excluding this condition in all nervous patients. It is highly important for many patients markedly underweight to take certain articles of diet for which they express some repugnance. A few moments of quiet talk may disclose some early experience which may be repressed but which can be helped.

I know of no greater fear for many patients than the dread of hemoptysis. I have seen a patient tremble so violently that the iron bedstead rattled when he had mistaken a few drops of saliva for blood. I am convinced that many of these patients fear death less than they fear beginning over again the prolonged monotonous nerve-wracking treatment. I have seen patients put cotton in the bottom of the sputum boxes in order to see more easily the slightest streak of blood in the sputum. I have seen others too nervous even to examine it themselves and ask the nurse to do so. The same fear often develops in regard to the bodily temperature. The thermometer has justly been called the "trouble stick." One of our patients in Saranac Lake wrote the following paraphrase:

"Who has not had the wild desire, to call his mouth  
thermometer a liar,

To smash it into bits and then remould it so it never  
could go higher."

There is no phobia more trying than this and it may so affect a patient that use of the thermometer must be forbidden or undertaken only by the nurse after advising the patient not to look at it.

These patients need psychic, not medicinal treatment. Such mental instability naturally affects the outlook and character of the patient, who may feel that he can never recover, can never be of use again in the world. This may lead him to rebel against the usual forms of treatment, failures, he calls them, to become a recluse, to refuse to see his friends and until psychic treatment is used he may fail in health.

I fully agree with the suggestion that all tuberculous patients

should be classified not only physically but also psychically. In every sanatorium are to be found a certain number of queer patients, some exceedingly nervous, some obsessed by phobias. Psychiatric treatment may be the only means of aiding their recovery from tuberculosis as well as from their mental maladjustments. In some instances the prolonged rest in bed may react in an unexpected manner. Instead of becoming less the patient becomes more nervous. He may see no end to it and so is further upset. If fever is still present in such a patient it may yet be wise to permit him to sit in a chair or if afebrile to suggest to him that he put on his clothes once a week and go for a drive or to the "movies." In this way, I feel, I have staved off numerous nervous spells.

The unexpected death of a patient in a distant city led me to inquire about the circumstances. The only explanation I could obtain was that the death from pulmonary tuberculosis of a friend with whom she had "cured" in Saranac Lake seemed so to affect her that although happy in her home, she quietly sank and died in a few weeks from cardiac failure without any cause for it being discovered. When a patient returns home to conditions under which she broke down in the first place, it is highly probable that she will break down again. In some instances the conditions are for her so intolerable that she dreads returning home. If the difficulty lies in the patient it may possibly be overcome; if in another member of the family, relapse must be expected unless strenuous measures can be taken to correct the condition.

The physician and his personality play an important psychological part in the treatment of pulmonary tuberculosis. Few men in tuberculosis work have had any psychiatric training and fewer still have any opportunity for using such knowledge in their busy lives. Many physicians are not suited to care for so chronic a disease as tuberculosis, though they may be excellent doctors for acutely ill patients. They lack strong personality, wide sympathy, keen understanding, great tact, discerning discretion, or a sense of humor. They can possibly maintain discipline but have no ability to develop it into self discipline in their patients. Self reliance as well as knowledge, ability to say no when necessary as well as yes, must be instilled into the inner consciousness of the patient. A psychological

aspect not always considered is the health of the sanatorium physicians. It is poor psychological treatment to have a physician suffering from tuberculosis and looking it, visiting patients who wonder whether they or he may succumb first. It is also a wise thing for different members of a staff to endeavor as far as possible to say the same thing to the patients, for conflicting statements may be most disturbing. A "natural" physician, is one who understands the patient's personality, who realizes that deception of the physician is part of the overcompensation, who can inspire hope and confidence which stimulate the circulation and increase the metabolic processes. The patient with pulmonary tuberculosis, Munro says, fights for life upon his stomach which is aided by a stimulating personality, depressed by even a fine physician with a gloomy outlook.

Some would have us believe that the tuberculous patient leads a libidinous existence for they say the sexual appetite is much increased. There is every reason why it should be. Lack of occupation, juxtaposition with attractive women placed under similar conditions, many hours of rest in invigorating air, a full, stimulating diet, high nervous tension breed dynamite, as a friend of mine put it, and a spark or "sparking," explodes it. I cannot believe that consciousness of a grave illness or a desire to drain life to the uttermost plays much if any part in indulgence. Fishberg states that the patients in a German sanatorium accused the resident physician of putting aphrodisiacs in their food—probably as a joke. Marriage may be the hymeneal altar upon which the newly married males immolate themselves but usually a friendly word of warning prevents this but rarely ever postpones the marriage. Worry over the fact that she may not be able to have children or more children is present in some women. The unfaithfulness of the spouse may be the undoing of others. Meeting a person apparently more attractive for the time being than the fiancé at home is the cause of other psychological troubles. The mental conflict of having the old lover walk the plank and taking up with the piratical new lover, who "understands" her problems so much better, is most disturbing to the patient and interferes with her recovery. Wet dreams, due to continence, require explanation in order to keep some patients on an even psychological keel.

## PSYCHONEUROSES

Psychoneuroses are rarer in the tuberculous than tuberculosis in the psychoneurotics. In order to determine whether the tuberculous poison is in any way connected with the occurrence of these mental conditions in tuberculosis, it is necessary to know if they occur more frequently in tuberculosis than in the general population. I am given to understand that psychoses occur in the general population in the proportion of about five new cases in 1,000 persons or about 0.5 per cent. In a study of 4,500 patients at the Sea View Hospital, McSweeney found a similar percentage, and in 8,878 patients at the Trudeau Sanatorium the percentage was again the same. This suggests, of course, that tuberculosis has little to do with the development of such mental conditions and also that in the general population other factors act to produce a similar number of cases. It is questionable if Clouston is correct in his opinion that tuberculosis does act as a causative factor in the psychoses, explaining the fact that so little of it is seen in the sanatoriums upon the assumption that when caused by tuberculosis the psychoses develop so rapidly that the patient is sent at once to the hospital for the insane and not to the sanatorium. It should be recalled, however, that Forster and Shepard found among the 100 patients they studied at the Cragmor Sanatorium two with dementia precox and two more with such a trend. It is highly probable that a certain number of similar cases were present among the patients both at Sea View and at Trudeau but as they did not require confinement for their mental abnormality they were not noted in the figures given, which relate in all probability only to those committed to the hospital for the insane.

When both tuberculosis and insanity are present in the forebears both diseases are more likely to occur, due to heredity and infection. When individuals have habits, as Worden states, which lead to mental disorders, such as moodiness, seclusiveness, suspiciousness, etc., really a structural defect in personality, and fall ill of clinical pulmonary tuberculosis, true psychoses are more likely to occur. These would include manic-depressive insanity, dementia precox and psychoneuroses.

Another type of psychoneurosis which some would connect more closely with tuberculosis is characterized by suspiciousness, delusions

of persecution, directed usually against those in immediate contact with the patient. In these cases a son may turn against his mother and demand to examine all articles of food before he will venture to eat them. Or again a patient may become suspicious of his former friends, accuse them of plotting his downfall. Later his suspicions may be connected with his food and cramps which frequently develop at night (not due to intestinal tuberculosis) are due, he thinks, to poison in his food. When possible to do so without detection he will exchange his plate or his glass of milk for that of his neighbor! Whenever he dines at a restaurant he is free of cramps.

A brief history of one case might put the matter more clearly:

Some twenty years ago I was consulted by a man, then aged forty-seven years, an important employee of one of the business houses in a large Eastern city, who stated that he had been told he had pulmonary tuberculosis. The diagnosis was easy to confirm as he had involvement of the whole of the left lung with signs of a cavity below the clavicle and of the upper half of the right as well. Tubercle bacilli were found in the sputum. He has had cough and expectoration most of the time from the onset of his illness in 1911 to the present. An occasional hemoptysis has occurred. On the whole he has done fairly well considering the amount of involvement present at the outset. Some ten years ago he gradually became suspicious of his friends and suspected them of trying to injure him and to force him to leave Saranac Lake. He convinced his family that he was subjected to persecution and pleaded with me to confront him with various persons about town. The policeman he thought looked at him in a queer way and he felt that he was under suspicion. Nothing would do but that I should speak to the officer, who naturally laughed at the foolish idea. He was a Hebrew and when at the synagogue some of his fellow worshipers spoke to him he again became suspicious. Some five years ago he began to dwell less on the cabal formed by his enemies to drive him out of town and to emphasize more and more that the many boarding housekeepers were poisoning his food. He moved from place to place with such painful frequency that I began to fear, as he did with me, that there would soon be no more places for him to try. Time and again he would entreat me to bring him face to face with some of the landlords. One day I finally did so and had on my hands one man mad and another certainly angry. Of course, no benefit came of it. During this time he would suffer from violent cramps at night and could not sleep if he ate at the table. But if he went to one of the restaurants in town he could eat a hearty meal, sleep well and feel well the next morning. For a time he purchased articles of food and ate them in his room, locking them between meal time in his trunk. He would occasionally, when he could do so without detection, exchange his glass of milk for his neighbor's. When it was called to his attention that the landlord was anxious to keep him as a guest and had no reason to try to poison him or to put him to bed which would entail more work, he maintained his ground that there was a plot to kill him. All this time he showed no signs of any desire for personal violence but simply wanted his evil wishers confounded and himself let alone.



Jealousy may at times be so exaggerated that it becomes a psychotic perversion. One patient confessed that he spat upon the floor so that his wife might contract the disease. A physician is mentioned (Munro) who compelled his wife to drink a glass of champagne in which he had spat. Another wife was forced to receive into her mouth sputum from the mouth of her husband. Had these patients lived at a time when the suttee was in style such conduct would not have been required to accomplish their purpose.

## THESES

1. In the literature concerning the *mental states* in pulmonary tuberculosis contradiction contradicts contradiction.
2. The sanatorium according to some should be an abode for saints, according to others a penal institution.
3. Few articles have been based upon recorded observation, many upon the imagined experience of the writer.
4. The mind is part of the body.
5. The psychiatrists believe that personality defects, slight or marked, are of great significance in the etiology of pulmonary tuberculosis; the tuberculosis expert usually unwisely ignores them.
6. In the complex life of today psychic injuries are so frequent and varied that few escape them, but they affect profoundly only a small proportion of the population.
7. When such an individual harbors a latent tuberculosis, the psychic injury may be sufficient to change infection into clinical disease.
8. The compensatory reactions to such injury may act similarly.
9. The reaction of any patient to tuberculosis depends upon what his personality was before the onset of the tuberculosis.
10. This reaction may range from slight nervousness to a definite psychosis.
11. The psychological problem begins with the diagnosis of tuberculosis and in some instances extends through the rest of the life of the patient.
12. His reaction on learning of the diagnosis may determine the future plan of treatment.

13. Very few patients are temperamentally unsuited for institutional treatment.
14. All patients should be classified according to their psychic as well as their physical state.
15. The majority of all patients with pulmonary tuberculosis are normal mentally.
16. Neuroses occur as frequently among the early cases as among the far advanced.
17. The reaction may be different in private patients who pay and public patients who do not.
18. An attempt to overcome the compensation against fear by stressing the dangers of the disease may result disastrously.
19. Suggestion and persuasion are powerful allies in the treatment of pulmonary tuberculosis.
20. Many unpleasant symptoms are amenable to suggestion.
21. The various phobias demand immediate psychic treatment.
22. It is better to grant slight liberties to a bed patient than to lose all the benefit of bed rest.
23. A return to a state of psychic turmoil at home means usually a speedy return to the cure.
24. Upon the personality of the tuberculosis expert rests much of the success of treatment.
25. The tuberculous patient reacts to the sex impulse like a normal person under similar conditions.
26. Psychoses requiring commitment to a hospital for the insane are not more frequent among tuberculous patients than among the general population.
27. Insane jealousy may occur but rarely does.

I wish to thank Dr. C. M. Anderson for many suggestions in the preparation of this article.

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# REST—ITS PLACE IN THE MANAGEMENT OF PULMONARY TUBERCULOSIS\*

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AT THE risk of courting the charge of attempting to carry coals to Newcastle, we come to bespeak the necessity of utilizing to even a fuller degree, the benefits deriving from the application of postural rest in the management of cases of clinical pulmonary tuberculosis. We cannot feel any sense of inappropriateness in presenting the subject on this occasion. On the contrary, we know of no more fitting place in which to stress the merits of this mode of treatment than here where the immortal Trudeau first reapplied and practised the principles enunciated by Detweiler and where the tradition has been so faithfully carried on by his colleagues and successors.

Phthisiologists of world wide reputation have for years accorded to rest a full measure of recognition and acclaim. Indeed, it is one of the oldest and most universally applied remedies we possess. It is the one great common denominator running through all schools of therapeutics and practice. It is the central theme upon which have been elaborated many variations, and from which have originated certain digressions. Climate, diet, heliotherapy, surgery—all have achieved a rank of importance in the armamentarium of the modern phthisiologist. Each has its school of enthusiastic supporters, some indeed seeking to extol the merits of the one to the partial exclusion of the others. Yet, it will invariably be found that no matter which of them has been used, rest also in some greater degree has been employed. Without the utilization of rest, it is extremely doubtful whether any of the other measures would prove lastingly effective.

A survey of the field of therapeutics today would, we believe, betray in certain places a feeling of impatience with rest as a practical measure of treatment and a tendency to speed up the whole course of treatment. We are living in a faster age, and youth especially—among whom most of the victims of tuberculosis may be counted—is exceedingly impatient of restraint. We discern, therefore, a tend-

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\* Delivered as part of a Symposium at the National Variety Artists Sanatorium, Saranac Lake, New York, on May 29th, 1932.

ency to get away from the old tried principles of rest and to pursue any course which gives promise of relief of symptoms and permanency of cure in the shortest possible time. Nor has the desire for speeding up the course of recovery been confined to lay groups. Medical groups, quasi-medical groups, and health organizations have fallen victims to the prevailing mode for accelerated tempo and are proclaiming ways and means of effecting more speedy recovery;—as witness the radical programs inaugurated in certain large municipalities in this country and the front page ebullitions of those incorrigible enthusiasts who would have us believe for instance that in surgery *alone* there has arisen a new and wholly effective method of achieving permanency of cure.

Certainly, no one will quarrel with the highly laudable desire to shorten the length of cure provided there is a reasonable assurance that in the end there will be a cure. The regulation rest-dietetic-hygienic regime is tedious and prolonged—a tax on patience and on purse—a great economic loss, if you will, and any measure or measures that will naturally lift the burden are to be thrice hailed and assiduously cultivated. To date, however, there has not been one such measure offered on a factual or experimental basis which either does not stem directly from the principle of rest or in closest co-ordination with it. For after all, nature takes just so long to accomplish her job—that of permanent healing—and beyond a certain point cannot be forced. The whole physiology, the whole mechanism of healing compels immobilization of the injured tissues for a certain definite given period. All we can do is to devise ways and means, methods and measures, of assuring more completeness in degree of immobilization or rest imparted to the injured tissue.

It is exactly in this manner that surgery has come so notably to our assistance. By a variety of methods—through surgery—we are succeeding simply in bringing about a greater degree of rest to the diseased part than was ever before found possible. All are but extensions or amplifications of the basic rest idea. Of course, each of these operative procedures is on a firm basis of merit. Their application will undoubtedly be greatly extended and rightfully so, for the philosophy underlying them—intensification of rest to the injured part—is fundamentally correct. We are only on the threshold of vast possibilities of further extension in their scope of usefulness.

In this our first flush of enthusiasm over the prospects spread

before us in the field of surgical assistance, let us not be blinded by the brilliancy of the results achieved thereby and let us not overlook the opportunity that lies constantly so close at hand toward effecting recovery by the application of strict postural immobilization. In our great zeal for utilizing the newer procedures, there lies this very real danger. Already some of our ill-advised colleagues are talking of curing all tuberculosis by surgery. Unless a warning is issued many a case perfectly capable of complete healing through postural bed rest will be operated upon. Should this come to pass irreparable damage will be done to the whole field of therapeutics, let alone to surgery. In this disease, if in no other, the ultimate direction in the management of the case must remain in the hands of the internist. The very key to success in the application of surgery to the treatment of pulmonary tuberculosis lies in the knowing and skilful selection of cases, whether it be by the aid of any specialized system of classification or otherwise. Such skill and knowledge can be acquired only by years of critical observation of innumerable types,—through varying phases, nuances, and reactions. None but the internist is likely to acquire or possess such experience and knowledge.

Even in cases where surgical assistance must be called upon, it should be clearly recognized that such assistance is but an aid to the cure—not the cure itself. Operative procedures, then, should be reinforced and supported by bed rest for some considerable time thereafter, and should not be considered a substitute for further rest. At the completion of the operation, while the injured lung or part thereof may be reduced to a state of thorough immobilization, the body as a whole, and every one of its organs, is still struggling under the burden of the toxemia of the disease and must be given sufficient time to recover. And, all familiar with this disease know that such time is not short.

Let us by all means utilize to the fullest degree then all that surgery has to offer in assisting us to restore health to our patients. Let us select our cases for operative interference only after due, careful, and, if necessary, prolonged consideration. Above all, let us not forget that a somewhat larger percentage of our patients can still be restored to economic usefulness by the continued stern, unrelenting application of horizontal bed rest followed, after full healing has been effected, by graduated exercises. Prudence is still a virtue in medicine as in all other things.

# CLINICAL MANIFESTATIONS OF RHEUMATIC FEVER\*

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UNTIL recently arthritis was considered the predominant manifestation of rheumatic fever; all other localizations of the infection were looked upon as complications. A complete change of view has occurred since Pappenheimer and Von Glahn<sup>1</sup> demonstrated widespread pathologic changes in the blood vessels and perivascular spaces throughout the body, and clinicians emphasized the large number of manifestations which are as characteristic of rheumatic fever as are the joint symptoms. We now regard rheumatic fever as an infection with varied and widespread localizations involving chiefly the circulatory system, but affecting also the other tissues and organs of the body to a greater or less degree. That arthritic manifestations are more conspicuous than others is due not so much to their relative frequency as to the ease with which they are recognized.

The disease is similar to syphilis and tuberculosis in many respects. Like these, it is chronic, it has periods of exacerbation and remission, and its effects are widespread, although it tends to localize in certain areas. Like syphilis with its specific tissue reaction, the gumma, and tuberculosis with its specific tissue reaction, the tubercle, rheumatic fever has its specific tissue reaction, the subcutaneous nodule or Aschoff Body. Modification of this reactive lesion is in the kind of tissue affected. However, its general character is everywhere similar. It is closely related to the nature of the tissues involved, as the vasa vasorum of the aorta and the small branches of the coronary, the mesenteric and other arteries. The compression of these vessels is seen in focal anemia and reactive panarteritis, and the replacement of the elastic tissue of the involved organs by fibrous tissue. These are the clinical manifestations of the disease.

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disease. Tissue reaction close to serous surfaces produces the exudative phenomena that occur in synovial areas, pleura, peritoncum and pericardium. In this respect again rhoumatism is similar to tuberculosis.

Depending upon what body tissues are most severely affected, the following outstanding clinical forms of rheumatic fever occur: a) Cardiac, b) Arthritic, c) Muscular, d) Nervous, c) Pseudo-surgical, f) Septicemic, and g) Respiratory. However, none of these forms is sharply defined for in each certain manifestations belonging to the other forms occur simultancously or at other times.

#### CARDIAC FORM

The heart is the most frequent scat of rheumatic disease. Nearly all cases of rheumatism are associated with some cardiac involvement, and in many it appears to be the only organ affected. Like tuberculosis with its predilection for the lungs, rheumatism has its predilection for the heart. All rheumatic cardiac disease is essentially a pancarditis, but the various layers of the heart are usually unevenly and unequally affected. As a rule the valves are most affected. Rheumatic carditis may go on for weeks or months without being recognized especially if no other rheumatic manifestations occur. The only evidence of its presence may be a simple tachycardia out of proportion to the degree of fever. The condition is usually recognized only when sufficient damage is done to produce gross clinical abnormality, such as cardiac enlargement, myocardial failure, valvular lesions, and so on.

In many instances cardiac involvement comes on with fever, or with increase of fever already present. Precordial pain of varying degree may be complained of often associated with palpitation, or with dyspnea and precordial discomfort. In more severe and acute forms, cardiac dilatation, marked dyspnea, orthopnea and signs of congestive heart failure become evident.

The objective phenomena of cardiac involvement, like the subjective symptoms, vary with the extent and the site of maximum damage. A diffuse precordial impulse and wave-like spread of ventricular contraction may be seen and felt. The character and rhythm of the sounds may change; muffling, splitting, reduplication and gallop rhythm may occur. When marked failure develops, tick-



tack rhythm or embryocardia is found. Various disturbances of sequential rhythm are common. Of these the most frequent are premature contractions, occurring singly or in groups, producing pulsus bigeminus, pulsus trigeminus, and so on. Paroxysmal tachycardia, nodal rhythm, shifting pace-maker, various degrees of heart block, auricular flutter and auricular fibrillation may occur. In the acute and subacute stages, an outstanding feature is the changing character of these various phenomena, especially changes in the type of arrhythmia and in the degree of block.

Usually the earliest indications of valvular damage are muffled apical sounds, which probably denote edema of the mitral or aortic leaflets, and the gradual onset of murmurs. In mitral valvulitis, a systolic murmur may be heard first at the pulmonic area or along the left sternal border, and only later move to the classic location and show the characteristic transmission. The onset of aortic valvular damage may be heralded by a basal systolic murmur, associated with the development of a suggestive Corrigan pulse, high pulse pressure, pistol shot and capillary pulsation, before the definite soft diastolic murmur, characteristic of aortic insufficiency, is detected. A transient to-and-fro friction rub may be the only indication of pericarditis.

The final result of the severe forms of acute carditis are the chronic cardiovalvular lesions with reactive cardiac hypertrophy, the more or less fibrous myocardium and fibrous adherent pericardium. These represent the scars left by previous inflammation of the heart and therefore should not be spoken of as chronic endocarditis, chronic myocarditis, or chronic pericarditis, unless there is evidence of an inflammatory process going on at the time of examination.

The electrocardiogram is a great help in the detection and the diagnosis of myocardial damage, even of the milder grades. We can discover by its aid the earliest stages of auriculoventricular and intraventricular conduction disturbance. Changes in the R-T and the S-T segments and in the T wave, as well as slurring and notching of the QRS complex, all of which indicate myocardial damage, are often present long before any other clinical evidence of heart involvement. Many of the disturbances of rhythm can be detected only by the electrocardiogram.

## ARTHRITIC FORM

There is no need to discuss at length this type of rheumatic fever. The pain, heat, tenderness, swelling and redness about the joints and the migrating character of the joint involvement, make this form of the disease easily recognized. Special mention may be made of a rare form of spinal joint involvement in rheumatic fever. Stiffness of the neck and a positive Kernig sign may occur and these together with fever and leukocytosis may produce a clinical picture simulating meningitis. The differential diagnosis is easy if the condition is thought of and care is exercised in making the examination.

## MUSCULAR FORM

Next in frequency to the arthritic form of rheumatic fever comes the form characterized by various aches and pains other than arthritic and localized contractures. So-called "growing pains" may be the only outstanding symptom of the disease. Other manifestations, such as fever and carditis, may be so mild that only the most careful examination will discover them. We must bear in mind that an occasional torticollis, pleurodynia, lumbago, intercostal neuralgia, or other pain and unexplained temporary contracture of muscles, especially in childhood, should be looked upon as warning signs of the possible presence of one of the most dangerous and crippling of diseases.

## NERVOUS FORM

Chorea is the most frequent manifestation of the nervous type of rheumatism. It is easily recognized even in the mildest form. Instances of primary cerebral rheumatism have been described. These are characterized by various forms of psychosis which may be accompanied by increased pressure of the cerebrospinal fluid, exaggerated reflexes, mydriasis, sluggish pupillary reflexes and symptoms of intoxication. A case of this type is reported by Tarragola.<sup>2</sup> The condition must be distinguished from the psychosis which occasionally results from digitalis therapy, an example of which was recently observed at the Coney Island Hospital. The patient was a woman, forty-two years of age, with old rheumatic mitral stenosis and auricular fibrillation who had suddenly developed decompensation and pulmonary edema. Massive doses of digitalis restored compensation,

but while under full digitalis effect, she developed peculiar delusions and hallucinations which disappeared as soon as the drug was discontinued. Idiosyncrasy to salicylates is said to be exhibited in some cases by similar mental states.

Grcnet<sup>3</sup> cites cases of psycho-encephalitis and Ménière's syndrome, rheumatic in origin. I saw a girl twelve years of age with old mitral stenosis and insufficiency who had had for several weeks severe headache, slight rigidity of the neck, low grade fever, and general body pains. Meningitis was suspected but was ruled out by spinal fluid examination. She subsequently developed definite signs of pericarditis, pleural effusion, and mild arthritis. Peripheral neuritis and various motor disturbances are often observed during the course of the disease.

#### PSEUDO-SURGICAL FORM

Under the pseudo-surgical form are grouped cases with symptoms which are often mistaken for primary surgical conditions. They are characterized by the gradual or sudden onset of diffuse abdominal pain which may soon become localized in the upper or lower quadrant and be accompanied by vomiting, local tenderness, rigidity, leukocytosis, and fever. Some are diagnosed acute appendicitis, cholecystitis, or peritonitis and frequently the patient is operated upon. At operation no disease of the abdominal viscera is discovered. Later the correct diagnosis is established by the development of typical rheumatic manifestations, for instance, arthritis and carditis. Interesting cases of this kind are reported by Gassinger and Costedoat,<sup>4</sup> Hyman,<sup>5</sup> Baudet,<sup>6</sup> and others. Recently I saw a seven year old child with chronic rheumatic cardiovalvular disease who gave the history of having been operated upon three years before for some acute abdominal condition, presumably appendicitis. At operation no abnormality had been found. The child subsequently had been confined to bed for several weeks because of unexplained fever, occasional nosebleed, and weakness. She recovered from this illness but the valvular heart disease was a silent witness to a pre-existing rheumatic disease making it altogether probable that the so-called "surgical abdomen" of three years before and the subsequent mysterious fever had been manifestations of the rheumatic infection. A noteworthy case of peritonitis of rheumatic origin is recently de-

scribed by Wood and Eliason<sup>7</sup> who at the same time give a complete summary of the literature of these conditions, beginning their review as far back as 1839. In many of the cases in which no intra-abdominal disease is found at operation, the abdominal pain, tenderness, and rigidity may be due to involvement of the abdominal muscles by the rheumatic infection. Involvement of the esophagus is an interesting, though rare, form of the disease. A case is reported by Grenet.<sup>3</sup> Dysphagia and fever, lasting fifteen days, were the only outstanding symptoms. Roentgen ray examinations revealed deviation of the esophagus to the right and a mass at the aortic portion of the tube. The affection cleared up under treatment with salicylates.

#### SEPTICEMIC FORM

Under the septicemic form are included those cases characterized by unexplained fever persisting for weeks and accompanied at times by fleeting pain in various parts of the body, malaise, occasional headache, weakness and drowsiness. Occasionally a subcuticular rash resembling rose spots appears. These cases may remain undiagnosed for weeks. The absence of a positive Widal reaction, of leukopenia, of a positive blood culture and the presence of a rapid pulse exclude the typhoid group of infections. Miliary tuberculosis, cryptogenetic sepsis, and subacute bacterial endocarditis are more difficult to rule out. The last named disease is especially difficult to exclude when there is pre-existing chronic valvular disease. The absence of the extracardiac manifestations of subacute bacterial endocarditis, such as enlarged spleen, embolic phenomena, especially petechiae, tenderness of the xyphoid (stressed by Libman), absence of red cells in the urine and repeated negative blood cultures, is important evidence against its presence. Absence of definite respiratory symptoms and signs, negative sputa, and negative roentgen ray findings, may rule out miliary tuberculosis of the lungs. Points that may clear up the diagnosis are the discovery of subcutaneous nodes, the development of unexplained pleural exudate and the response to salicylates.

#### RESPIRATORY FORM

Acute or subacute inflammation of the tonsils and pharynx is a feature common to nearly all cases of rheumatic disease. Occasionally, we find a localized pleurisy or a curiously migrating pneumonia

as the only manifestation. Many cases of rheumatic pneumonia are described in the literature. In a recent paper on the pathology of rheumatic pneumonia, Gouley and Eiman<sup>8</sup> give a complete description of the condition and review the literature. They note that Fuller described the condition as long ago as 1854. Of more recent writers, they quote Thayer, Swift, Rabinowitz, and Paul.

Noteworthy features are nosebleed and hemoptysis. In children especially nosebleed may at times be the first manifestation of respiratory rheumatism. Hemoptysis occurring in a patient with chronic mitral stenosis but without any other active rheumatic manifestation may perhaps alone be evidence of rheumatic activity. It suggests fresh involvement of the pulmonary vascular tree, which together with the increased pulmonary arterial pressure common in mitral stenosis may result in the rupture of vessels. I have recently seen two cases of chronic mitral stenosis showing this symptom and both had a low grade fever. One later developed mild arthritis, the other active carditis. The recognition of this possibility may save an occasional patient with this symptom from further damage by inappropriate treatment.

#### AIDS IN DIAGNOSIS

Patients presenting any of the symptoms described above which are suggestive of a rheumatic infection should be carefully observed and investigated. The investigation should include a search for other evidence of the disease such as subcutaneous nodes, cutaneous manifestations (the most common of which is erythema multiforme), nose and throat manifestations (as tonsillitis, pharyngitis, and nosebleed), nutritional disturbances, constitutional weakness, sweating, and changes in the blood picture. The most frequent change in the blood picture are various grades of secondary anemias and a slight or moderate leukocytosis. Increased sedimentation rate of the red cells is helpful.

The most important diagnostic aid is careful observation of the temperature. All active cases of rheumatism, regardless of how mild they may be, will show some rise in temperature at one time or another during the day or week. Every suspected case, therefore, should have the rectal temperature taken and recorded at least three times a day for many days. It may be found normal at certain times of

the day, but will be elevated at other times. In the presence of suggestive symptoms and signs any rise above the maximum normal of  $99.6^{\circ}$  is significant.

### CONCLUSIONS

The important facts I wish to emphasize are these. Rheumatic fever is an infection with widespread manifestations which may stealthily and in disguise invade and cripple the human organism. The organ most often affected is the heart, but no organ of the body is always spared. According to the predominant seat of involvement, there are distinct forms of the disease which require careful diagnostic differentiation from other diseases. The frequency with which we find chronic rheumatic heart disease in the young when there is no history of a previous rheumatic infection demonstrates how often the various manifestations of rheumatism are overlooked or misinterpreted. The clinical forms of the disease enumerated in this paper are easily recognized but there may be still other forms which are not yet clearly distinguished. Nephritis occurring in childhood with upper respiratory infection with or without clinically detectable cardiac manifestations, may perhaps be rheumatic in origin.

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# DIGITALIS ADMINISTRATION\*

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THE digitalis glucosides, all of which are closely related chemically although they are obtained from very different botanical species, have certain pharmacological properties in common. Some of them are more lasting in their effects, others more prompt and transient. In relation to their effectiveness upon the heart some of them cause more nausea than others. But the most remarkable fact about them is that although over a dozen different plant glucosides have been discovered and innumerable purified products prepared and marketed, the powdered digitalis leaf which Withering advocated a century and a half ago is still the form preferred by nearly all experienced practitioners. Although quinine and morphine have supplanted cinchona bark and opium, the pure glucosides from foxglove and similar glucosides from other plants have not yet been found superior to the crude drug.

Because digitalis is still given as the crude drug, and because chemical tests for glucoside content are unsatisfactory, the potency of each lot must be determined by trial on patients, or by observing the effects on animals. Frogs, mice, dogs, cats and pigeons have all been used to test the strength of digitalis preparations. Most widely accepted are the frog and cat methods, which are now used in many countries to standardize these drugs. The object of assay is the same whether one uses a chemical method, as is done with opium and belladonna, or a biologic test as is necessary with digitalis. Careful chemical assay, properly checked in duplicate, or biological assay carried out with many animals, serves to control the potency of the marketed product and provide the physician with a preparation of sufficiently uniform strength. There is no more reason for marketing digitalis in "cat units" than for marketing opium in "acid units." One is assayed with cats, the other with acid and an indicator, but the object of assay in either case is to control strength

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so that each gram of drug, obtained anywhere and at any time, has a constant potency.

The physician must remember that errors in assay or in preparing doses may occur,<sup>1</sup> and that patients vary widely in their susceptibility to the drug. When given intravenously to dogs or cats the fatal dose, for the most sensitive animals, is only one-third that which is needed for the most resistant. In patients there is the added variability of absorption, so that the latitude is even greater and one patient may tolerate, without evidence of drug action, four or five times the dose, per unit of weight, which causes severe toxic symptoms in another.<sup>2</sup> The size of the initial dose, and the size and frequency of subsequent doses must be adjusted to insure drug effects in the most refractory patient, and to avoid serious toxic symptoms in the more susceptible. Having a preparation of constant strength facilitates the physician's task, but he is never excused, by ignorance of the strength of a preparation, for failing to obtain full therapeutic action or for producing toxic symptoms.

The effects of a dose of digitalis reach a maximum six to ten hours after oral administration, and do not wear off for several days. The drug should be given at six to twelve hour intervals when medication is begun, but need not be taken more often than every forty-eight hours to maintain its effect. Gelatin capsules or properly prepared pills, containing 0.1 to 0.2 Gm. of powdered leaf, offer the best mode of administration. Tinctures keep their potency well, but must be measured out of a properly marked dropper in order to insure correct dosage. Counting the number of drops delivered by the conventional dropper is a troublesome and inaccurate method, and the number of drops, per cubic centimeter of tincture, may vary from 25 to 60. An effective and inexpensive method is to use only 0.2 Gm. pills or capsules and regulate the daily intake by the frequency of dosage. If patients require less than 0.2 Gm. daily, one pill given three to five days per week will maintain a sufficiently constant effect with minimum cost and inconvenience.

With a preparation of standard strength, the initial dose should be from 0.5 to 0.8 Gm., depending on the patient's size and the need for rapid effect, and subsequent doses at intervals of six to twelve hours should be based on the condition of the patient. In auricular fibrillation, when a rapid ventricular rate is present, the size and



frequency of subsequent doses depend on the effect of the initial dose in reducing the pulse rate. In patients with regularly beating hearts, loss of appetite, slight nausea, prolonged A-V conduction or coupled beats are the only sure evidence that the maximal therapeutic effect has been passed. If any of these manifestations occur the drug must be withheld until they disappear and have been absent for at least one day, and then smaller or less frequent doses given to maintain the therapeutic effect. Naturally, if an excellent effect on diuresis and cardiac signs and symptoms is attained without causing toxic symptoms, the dose of the drug has been adequate and smaller maintenance doses can be given. As a rule one can rapidly saturate the patient by giving 0.5 to 0.8 Gm. as an initial dose, and 0.2 Gm. every eight to twelve hours so long as none of the toxic symptoms appear. The anorexia and nausea produced by digitalis is usually accompanied by a sense of dizziness and fulness in the head which distinguishes it from the anorexia, nausea and vomiting of cardiac failure and hepatic congestion. When the massive dose method of administration is used, assuming a tolerance of 33 mg. per Kg. of body weight, complete saturation is obtained more quickly; but toxic reactions occur more frequently. If the preparation is unusually potent the massive dose method is sure to produce unpleasant and even alarming effects.<sup>1</sup> The need for rapid digitalis medication is rare. Severe symptoms of cardiac failure respond quickly to venesection or the oxygen tent, and much more slowly even to intravenous strophanthin. While strophanthin therapy, not only for emergency but for routine management of chronic heart disease, now enjoys an increasing vogue in Germany and Central Europe, it has not been widely used in America. If venesection and oxygen therapy are intelligently employed, rapid digitalis medication, with its risk of severe nausea or cardiac arrhythmia, is rarely needed. In many cases, indeed, it is sufficient to give 0.2 Gm. of powdered leaf daily, allowing cumulation of effects to give a satisfactory saturation in six to ten days. It is my belief that the maintenance dose should be large enough to give maximal effect short of toxicity even in those ambulatory patients to whom digitalis may be given over long periods of time to prevent or postpone cardiac failure. As with insulin, which has a therapeutic dose bordering on the toxic, so with digitalis, it is well for some patients to experience

the mild minor toxic effects and to keep the medication at a level just below that which causes unpleasant symptoms. In some patients, especially those who are unable to grasp the rationale of treatment with this drug, it is important to avoid even sufficiently intensive treatment to cause anorexia, because they cannot be persuaded to continue treatment, even in milder doses, after they have once experienced its toxic effects. It is, however, true that in some instances doses only half as great as can be tolerated will completely control the signs and symptoms of heart failure. In auricular fibrillation particularly the dose can be adjusted to the ventricular rate and often doses well below the toxic level are found to be adequate. When the heart is regular control is less simple and experience leads one to believe that the effect of the drug on muscular contraction increases steadily up to the level at which cardiac arrhythmias begin to occur. The best level of digitalis dosage, for the prevention or relief of congestive heart failure in regularly beating hearts, is just below the toxic dose.

Before discussing the types of disorder which are likely to be benefited by the use of this drug, and those which can be but little influenced by it, it is worth while to describe briefly the pharmacologic properties which are now well recognized. Digitalis increases the effect of vagus tone on the heart, which leads to slowing of the sinus rate and to a decrease of irritability and of the conduction time in the conduction system between auricle and ventricle. A high vagus tone also increases irritability and conduction rate in the auricular fibers themselves. The effect of digitalis on rhythmicity of myocardial tissues is negligible; the arrhythmias which arise from its use may all be ascribed to its direct effect in diminishing irritability and conduction time, thus facilitating re-entry of impulses, and the formation of circus movements. This direct effect on the muscle is most marked in hearts already damaged by fever or local organic disease, and thus contrasts with its vagal effects. The latter occur only when vagus tone is normally high, but in anemic, febrile or decompensated patients, or in those whose vagal tone is released by atropine, the drug has little or no effect on sinus rate. Its direct effect may cause heart block or ectopic beats. In animals digitalis produces an increase in arterial pressure and a decrease in return flow to the heart by diminishing the effective blood volume. These

effects are less striking in man, and the drug is of little value in raising the blood pressure of hypotensive patients or of those in shock. Finally, digitalis has a unique effect on the contractile phenomena in dilated or failing hearts but causes little change in the systole of normal ventricles. In failing hearts it shortens systole and increases its efficiency, so that the heart can maintain a larger volume of circulation with less expenditure of effort. The heart, when this property of the drug manifests itself, becomes smaller, venous pressure falls and cardiac output increases.<sup>3</sup> Digitalis acts not like a stimulus, whipping up an already overloaded muscle, but like a lubricant which permits a pump to work better, so that even with less energy applied more fluid is expelled per beat. In the normal heart the output per beat is dependent on the level of venous pressure, but in failure the venous pressure rises and the output may fall below the basal level. The normal heart can increase its output, per minute, to four or five times the basal level if the return flow is great, as in exercise. The failing heart cannot respond to greater loads, but after digitalis an abnormally low output may be elevated so as to more nearly approach the normal, and the response to additional rise in venous pressure, due to exercise, is improved. There is no evidence that digitalis decreases the capacity of the normal heart to respond to a rise in venous pressure with increased output, or that it increases the energy expenditure of the failing heart when it improves its contractile efficiency.

It is the effect of digitalis on the systolic efficiency of the heart which makes the drug valuable in treating congestive heart failure with regular rhythm. In experiments on hearts dilated by manipulation or by drugs this property of digitalis is regularly observed, but in human beings afflicted with different types of chronic myocardial disease an improvement in cardiac function does not always occur. If digitalis is administered to such patients and at the same time they are put in comfortable cardiac beds, on an adequate low-salt diet with a limited fluid intake, and given sufficient medication to keep them quiet, an improvement is noted in the great majority. But this improvement cannot be attributed to the drug alone. McKenzie was the first to study the action of the drug, given to patients who had been kept under proper conditions for some days before the drug was started and in whom it was possible to distinguish

between the effects of proper general care and the effects of the drug. Eggleston, Luten, and Marvin<sup>4</sup> have used this careful method and there are available about 100 reported cases with regular rhythm so treated. In patients with congestive failure due to non-valvular, degenerative, arteriosclerotic or involutional heart disease, digitalis had no demonstrable effect in improving the cardiac function of 48 per cent., there was definite amelioration of signs and symptoms after giving adequate doses of the drug in 52 per cent. In the group with congestive failure preceded by valvular heart disease, and in many cases by rheumatic myocarditis, only 31 per cent. were demonstrably better after a thorough trial of digitalis. In some instances of congestive failure with regular rhythm digitalis can so affect the heart muscle that a rapid and dramatic diuresis is produced followed by complete relief of the severe signs and symptoms of heart failure. This effect may be as striking as is ever produced by the drug in cases of auricular fibrillation. But in the majority of cases, the effect is imperceptible, and there can be no doubt that the benefit in the average case when the heart is regular is less striking than in patients with rapid ventricular rates due to auricular fibrillation. It is the rheumatic cases and particularly those with active rheumatic myocarditis which respond most poorly, and the predominance of this type in England led many to doubt the value of the drug in cases without fibrillation. When degenerative heart disease predominates beneficial effects occur frequently, especially in patients to whom the drug and good general care are administered simultaneously. These observations have convinced Wenckebach<sup>5</sup> and Christian<sup>6</sup> that the drug is almost as valuable in regular as in fibrillating hearts. It is well to remember that results cannot be predicted, that failure of digitalis therapy is not infrequent, but success which can be obtained in no other way is encountered often enough to make a trial of the drug worth while in almost every case of congestive heart failure. Even when congestive failure has not occurred, but when the response to effort is poor, and the enlarged heart shows by a gallop rhythm or an alternating pulse that it is laboring under a heavy burden, digitalis therapy may be of great value. In such cases the signs of heart strain and the symptoms of distress may be wholly relieved by continued digitalis medication. Under these circumstances a favorable response to digitalis is more

frequent than when the heart is more seriously decompensated. In patients with an enlarged heart due to hypertension or to other cause the heart may have been heavily burdened for a long time before definite evidence of failure appears. Some have advised that digitalis be given to these patients as a prophylactic against heart failure, to ease the overburdened heart. Obviously it is impossible even for the most skilful clinician to decide how soon a heart will fail, or for how long digitalis may have postponed failure. Large series of hypertensive cases, some treated with and others without digitalis, have not been studied in relation to the time of onset of failure. This form of digitalis medication is quite rational, and has been urged by men of experience.<sup>7</sup> The drug in such cases is given over periods of months or years, in doses similar to those used for heart failure although the digitalis effect may be induced more slowly. The same treatment has been recommended for patients with hearts of normal size, but with functional heart symptoms. This has little to support it, either in clinical experience or in the known properties of the drug.

Digitalis has the following effects on irregularity of the heart beat: 1. It may produce or accentuate the frequency of ventricular extrasystoles. 2. It may abolish ventricular extrasystoles already present. 3. In toxic doses it may produce partial or complete block between auricle and ventricle. 4. In complete and permanent heart block it either has no effect or slightly accelerates the heart rate. 5. It sometimes prevents paroxysmal auricular tachycardia, flutter or fibrillation. 6. It seems occasionally to precipitate auricular fibrillation in patients with advanced mitral stenosis, and it rarely stops but usually seems to prolong auricular fibrillation. 7. It occasionally stops attacks of auricular flutter. 8. Its great clinical value in cardiac irregularities is due to the fact that it slows the ventricular rate in auricular fibrillation and flutter; but it must be emphasized that it does not often end these arrhythmias and that it has little effect on the heart action when there is spontaneously a slow ventricular response to auricular arrhythmias. These actions of digitalis are due to the balance, varying in different individuals, between its vagal effect, which decreases irritability in the A-V conducting system and increases irritability in the auricle, and its direct effect upon the heart muscle which decreases irritability

in auricle and A-V system and to a lesser degree in the ventricle. The vagal effect of digitalis can be entirely inhibited by full doses (1/30-1/20 gr.) of atropine, but this is rarely indicated in clinical practice.

Ventricular ectopic beats seldom require treatment, but digitalis, given for concomitant heart failure, may abolish these abnormal beats and it may also abolish them when they occur in patients who have no other signs or symptoms of heart disease. Usually it is less effective than quinidin in controlling extrasystoles. In the three types of paroxysmal auricular tachycardia, simple tachycardia, flutter and fibrillation, the attacks can more often be stopped, and, if of frequent occurrence, prevented by quinidin than by digitalis. Occasionally patients refractory to preventive quinidin therapy are entirely relieved by constant digitalis medication. In auricular flutter of long standing digitalis in full doses sometimes converts the mechanism into fibrillation and later a reversion to regular rhythm frequently occurs. But this fortunate outcome of digitalis medication in auricular flutter is not regularly observed. In the majority of cases chronic flutter is rather refractory to treatment, with either digitalis or quinidin. Such refractory cases behave like those with auricular fibrillation, they have a high degree of A-V block and a slow ventricular pulse as long as they are kept on digitalis. The heart action may be adequate for the needs of a rather active life in spite of continuing flutter if the ventricular response is thus satisfactorily controlled by digitalis.

It is quite unusual for chronic auricular fibrillation to stop during digitalis treatment. When the drug is given to patients whose apex rate is over 140 the drug not only slows the rate but accentuates the irregularity of the ventricular response until the apex rate drops below 80. At rates lower than 80 the pulse and apex beat may appear to be regular and may show the same changes in rate during the respiratory cycle which occur in normally beating hearts. Throughout all these changes in the rate and in the rhythm of the ventricles caused by digitalis through its action on the A-V conduction system the auricular arrhythmia continues unchanged except that the rapidity of the electrical auricular oscillations are altered. The fibrillating heart, if it is originally so rapid that the irregularity is imperceptible, is apparently at first made "irregular" by digitalis

but later, when it is markedly slowed, it seems "regular" or "nearly regular." But the auricular fibrillation continues and the ventricles, except in rare cases of associated complete heart block, never beat with a regular rhythm. This is true whether the patient is untreated or has responded well to digitalis. The spacing of the apex beats is most uneven at rates of 90 to 120, above or below this range unevenness becomes less marked in proportion to the degree of acceleration or of slowing. The criterion of effectiveness of digitalis is not the degree of uneven spacing of ventricular beats, but the rate of the ventricle and the condition of the circulation. Digitalis should be given, if possible, until the apex rate drops below 80 at rest, and a constant ration sufficient to maintain this rate should be indefinitely continued. It is common for patients with auricular fibrillation to have a slow ventricular response due to spontaneous disturbance in A-V conduction. In such cases digitalis has a much less striking effect than in those with an apex rate over 120 per minute. Even when a very rapid rate is present before digitalis is given the rate may never return to the original level but may remain as low as 90-100 for months after digitalis is discontinued. In many cases the apex rate does gradually accelerate after digitalis is stopped. Within ten to fifteen days the effects of full digitalis action may wear off and then all the distressing symptoms of heart failure as well as the rapid and uneven heart beat may recur. Therefore, digitalis treatment of auricular fibrillation is always a strictly individual problem. Neither the size of the dose nor the necessary duration of medication can be prescribed routinely. The safest course is to continue the drug as long as any evidence of heart failure is present, and to begin it again if the apex rate rises above 80.

The rapid rate of the ventricles in auricular fibrillation is not invariably controlled by digitalis even when given in doses large enough to produce nausea and other toxic symptoms. Fever, severe congestive heart failure in chronic valvular disease, and hyperthyroidism are the complicating factors in most cases which are refractory to the drug. None of these conditions regularly inhibits satisfactory digitalis action. Many severe cases of hyperthyroidism with fibrillation respond perfectly to the drug in normal doses but it is true that sometimes hyperthyroidism does prevent ventricular

slowing and in the absence of fever and of valvular or coronary disease the failure of digitalis to slow the ventricular rate should suggest the presence of latent Graves' disease.

In every case of chronic auricular fibrillation the question of attempting to restore and maintain a normal sinus rhythm may be raised. The restoration of normal rhythm can be effected with quinidin in the majority of cases and the normal rhythm may often be maintained for months if appropriate doses of quinidin be continuously given. In a few cases, free from valvular disease, cardiac enlargement, or signs of congestive failure, quinidin may be given immediately. However, in most cases it is given only after digitalis and general care have produced all the improvement in the cardiac condition that may reasonably be expected. Patients with valvular disease, massive cardiac enlargement, or decompensation refractory to therapy are as a rule not benefited by having regular rhythm restored, and usually revert quickly to auricular fibrillation. In each case the decision as to the wisdom of giving quinidin must be based on a thorough study of the patient. In many instances continuous digitalis therapy will be preferred, or may have to be used, because of the failure of quinidin to maintain a regular rhythm.

Formerly many contraindications to the use of digitalis were described but hypertension, aortic insufficiency, or a permanently slow pulse due to heart block are no longer regarded as conditions in which the drug is harmful. If patients with these disturbances have evidence of heart failure, a trial of digitalis is justified and experience shows that gratifying results may sometimes be obtained in patients with aortic disease or heart block, and that improvement frequently occurs in patients with hypertension.

It must be emphasized, however, that many disorders in which digitalis has been used do not respond at all to the drug and some seem actually to be aggravated by full doses. The careful study of the effects of digitalis in pneumonia carried out on a large number of cases at New York<sup>8</sup> has been corroborated by an equally careful comparison of several hundred digitalized and undigitalized cases at Los Angeles.<sup>9</sup> In both series the digitalis-treated cases had a higher death rate. There is little rational basis for using digitalis in the treatment of a disease in which the death rate varies with the degree of bacteremia. Patients with pneumonia are often cyanotic and



dyspneic, but these symptoms are not cardiac in origin. They can be controlled by oxygen therapy, but not by the use of digitalis. The depression and nausea which occur in a small proportion of even carefully digitalized patients with pneumonia contribute probably to lowering resistance, and thus may lead to a higher death rate. On the other hand although the cardiac action of digitalis is demonstrable, still it is of no definite value in reducing mortality. Even in cases which are not intoxicated by digitalis the death rate following digitalis therapy is higher than in untreated cases. It is possible that digitalis glucosides interfere with the normal defense reaction against the pneumococcus. It is certain that in pneumonia death is due to vasomotor paralysis and not to cardiac failure.

In tachycardia without auricular fibrillation due to loss of blood, to postoperative shock, to fever, or to hyperthyroidism, digitalis is of negligible value. As a rule under these circumstances it has no effect on pulse rate or circulation. To prescribe digitalis hopefully in such cases would do little harm were it not for the tendency to postpone more difficult but more effective therapy until the drug has had time to act and prove its success or failure. Particularly in postoperative collapse, when time is of vital importance, the use of transfusion and saline injections should not be postponed in the hope that digitalis will tone up the circulation. In animals digitalis does minimize the effects of shock, but in man this action is so slight that more effective measures must be used. The correct procedure is to give digitalis, in pneumonia, shock, fever or Graves' disease, only if auricular fibrillation occurs, or if the heart, hypertrophied and failing, would indicate a trial of digitalis therapy even though the intercurrent or complicating condition were absent. Never substitute digitalis for more effective measures in patients with normal hearts when rapid heart rates or circulatory failure are due to extra-cardiac causes.

#### SUMMARY

Adequate and prolonged treatment with digitalis is of great value in auricular fibrillation with rapid ventricular rate. It is also of value but less regularly effective in congestive failure with regular rhythm. It is useful in the prophylaxis of heart failure in hypertension with cardiac hypertrophy. It is of negligible value in pneu-

monia and its occasional toxic effects may do harm. It is of no real value in treating the sinus tachycardia of acute anemia, of shock, of febrile disorders, or of Graves' disease.

Even though digitalis preparations of uniform potency be used the proper dose cannot be calculated in advance. It must be given in divided doses and the results carefully controlled so that full effects will be obtained without producing undesirable toxic symptoms.

The purpose of assay is to insure a uniformly potent drug, and this can be attained only by careful and intelligent biologic assay. Using cats for assay and labeling the strength in "cat units" is not necessarily a guarantee of uniform potency.

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# TREATMENT OF DIABETES MELLITUS

## Some Practical Considerations

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THE discovery of insulin in 1922 has made possible an increased breadth of therapeutic possibilities in diabetes mellitus. The ultimate object of treatment is in no way different today from what it was before insulin but the method of procedure must be different. One can say categorically that the major objectives in treating the diabetic patient are to keep him free from sugar and complications, and to return him to a fairly normal social and economic life. I do not believe that such a chemical problem as the return of the blood sugar to a constant absolute normal has anything to do with the major problem confronting us.

Before the days of insulin diabetics could roughly be classified into two main groups: in the one group the disease was of such a mild nature that it was possible to construct a diet furnishing sufficient calories to render the patient economically efficient and at the same time keep his chemical metabolism under control. In the other group the disease was of such a degree of severity that it was extremely difficult and sometimes impossible to attain a diet of sufficient calories for the individual to live. Included in the latter group were those diabetic patients whose tolerance for carbohydrate was so low that in order to furnish sufficient food many manipulations of the dietary proportions were necessary. It was particularly for this group of patients that the formula method of treatment became valuable. The formula method of developing diets was an attempt to apply chemical principles in a mathematical way to the construction of the diet. Perhaps the best-known chemical formulae were those of Woodyatt,<sup>1</sup> Wilder,<sup>2</sup> and Shaffer.<sup>3</sup> All these were carefully worked out to provide a balanced diet of sufficient calories to maintain a patient in nitrogen equilibrium without glycosuria or ketonuria. The FA:G\*\*

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\*\* FA = fatty acids; G = glucose.

ratio formed the keystone on which rested most of the mathematical-chemical calculations. It was interesting to note that the method of figuring and the final FA:G ratio varied with the different investigators. In a paper by Wilder and Winter the diet of sixteen patients was calculated according to their formula. In a paper published in 1922<sup>4</sup> I recalculated each one of these diets on the formulae proposed by Woodyatt, and Palmer and Ladd<sup>5</sup> and showed marked variations in the FA:G ratio. In other words, the same diet calculated on different formulae gave markedly different FA:G ratios.

It is particularly important to note that the basis of calculating a proper FA:G was "a clinically significant ketosis," and it is only fair to state that a clinically significant ketosis is a varying condition. Ketosis varies in its appearance even in the same diabetic patient under the same dietary conditions at different times. It is a well-known fact to students of diabetes that acetone may be present in some patients almost constantly without signifying clinical ketosis, and in other diabetic patients it may appear or disappear without any known change in the controllable factors of treatment.

Furthermore, it cannot be denied that in any attempt at accurate estimations of food intake on the basis of food tables one immediately meets with an incalculable percentage error. For that reason it has always seemed that the formulary method of treating diabetics was of more theoretical than practical value, and that if one actually wanted to regulate the diet of a patient on the basis of chemical formulae all food would have to be analysed. In tables of food values published by the United States Department of Agriculture, Circular 50,<sup>6</sup> one finds for instance variations in the carbohydrate content of some of the commoner foods as follows:

Bananas .....	15.4%—23%
Cherries .....	12.6 —17.8
Grapefruit .....	6 —11.2
Oranges .....	0.7 —11.2

Variations of such wide proportions would invalidate the use of an "average" when discussing chemical formulae.

Finally the advent of insulin has so broadened the possibilities of dietetic treatment that simpler methods of establishing diets are now readily available.

These objections to the formula method are intended to refer

entirely to the actual therapy of the individual patient. It must be apparent to any conservative observer that although a mathematical formula seems to be more scientific than a simpler clinical procedure, still in truth it may have more the appearance than the reality of science. From a practical point of view we believe that it is no more accurate to ration an individual diabetic patient on the basis of these general formulae with all their uncontrollable factors than it is to follow the simpler scheme which I shall outline below. As a matter of fact, occasionally one encounters a patient whose chemical disturbances are so great that they necessitate a thorough and completely individual investigation. In such instances the patient presents a problem in metabolic research.

Despite this criticism of the practical value of the mathematical formula method in present day therapy, I believe that the studies in connection with the development of these procedures have been of the greatest scientific value to our knowledge of the disease. Certainly Woodyatt's careful inquiry into the difference between fuel and food, his emphasis on the importance of distinguishing between endogenous and exogenous food metabolism, have had a profound and beneficial influence on our therapeutic procedures. In fact all the studies of that era must be considered pioneer investigations which have been of lasting benefit. It is merely my personal belief that at the present time such procedures are rarely necessary for treating an individual patient. We must distinguish between the science of the disease diabetes and the treatment of the diabetic patient.

#### TREATMENT OF THE MILD DIABETIC

Many of the diabetic patients who enter the physician's consulting room give a history of the accidental discovery of sugar in the urine on routine health or insurance examinations. Careful analysis of the history fails to give any evidence suggesting a long duration of diabetes. The family history may or may not indicate a familial tendency toward diabetes. In such patients there seems to be no need and no indication for elaborate procedures. Since both the history and the physical examination indicate that the patient is probably a mild diabetic, certainly the wisest procedure would seem to be an analysis of the food intake. This is best done by asking the patient

to keep for a week a diary of the approximate amounts of all food and drink taken, of exercise, condition of the bowels, and other data of the daily life. At the end of the week a study of the food intake will give a fairly close idea of the carbohydrate and total food values. A twenty-four hour urine analysis will show the amount of sugar excreted, and by the simplest possible mathematics the patient's approximate tolerance can be established. In many of these diabetics the disease is so mild that a rigid quantitative diet is impractical and unnecessary. If the food analysis indicates over-indulgence in any particular type of carbohydrate, removal or restriction of that alone will often result in a clearing up of the glycosuria. For the purpose of starting such a patient we have been in the habit of using a very simple sheet (see diet, on page 211). In the use of this sheet no attempt is made at exact measurements of the intake. The patients are told that they are to eat normal portions. We often use quantitative diet lists which give the exact food values in measured portions as well as the kitchen equivalent of these exact measurements. However it hardly seems necessary to make a mild diabetic bother with scales and weights, and we are much more likely to gain cooperation by the simpler method.

On the bottom of diet (on page 211) are blanks for potatoes, fruits, and bread. These are filled in according to our impression of the ability of the patient to use carbohydrate. It will be noted that there is no space on the chart for any of the so-called "special diabetic foods." Our experience with such foods has been distinctly unsuccessful. In general the special foods consist of two types. Most are breadstuffs containing a high protein flour made from such things as casein and soy beans. There is very little use at the present time for most of these high protein foods, since approximately 58 per cent. of the protein is available as carbohydrate. Whereas most of such products may be considered honest attempts at replacement, they are as a rule expensive. It is doubtful whether the amount of good obtained for the extra expense is worth the expense.

On the other hand, it has been our sad experience that many of the so-called diabetic breads and cakes which are labeled, "contain no sugar" contain a very high proportion of carbohydrate. The poor patient is deluded into the belief that by getting them at a fancy store and paying a fancy price he has obtained something that will

not harm him. Actually, of course, the use of such foods is distinctly contraindicated.

Reverting to the mild diabetic who starts with this simple scheme, he is instructed to return in a week again bringing his list of foods and a twenty-four hour specimen of urine. Analysis of these gives the status of the day. After two to four weeks of this type of observation the patient is pretty well sized up, and proper instructions can then be given so that he will not have to return more than once a month.

#### PROCEDURE IN DOUBTFUL CASES

Some patients come into the office in severe acidosis and others clearly indicate by the history and the physical examination that the intensity of their disease cannot be determined offhand. It is a matter of observation that the condition of a diabetic patient when he first presents himself depends not only on the severity of his disease but on the kind of treatment he has been receiving. The patient who consults a physician just after having left a well-known diabetic clinic may offer an entirely different problem in therapy from another patient with an equally severe diabetes who has been negligent about following the instructions given him. Many patients when they first come to a physician offer a difficult problem because of the well-known bad effects of poor treatment on the course of diabetes.

For a patient with diabetes of questionable severity who has had no previous training institutional assistance is almost, although not absolutely, necessary. How shall we begin to treat the unknown case? Is there a definite principle and a set rule which must be followed? Is there a particular proportion of foodstuffs in the diet to be given without which no good results can be obtained? A simple retrospect of the dietetic procedures in vogue during the past fifteen or twenty years, a comparison of these with the older methods of Naunyn and Von Noorden, a follow-up of the patients subjected to various procedures at the Joslin Clinic will answer these questions with little doubt. Certainly the various procedures advocated have differed widely both in principle and in practice. Yet the starvation method of Allen,<sup>7</sup> the comparatively high fat, low calorie diet of Newburgh,<sup>8</sup> the formula method—all of these give good results in the hands of men acquainted with the disease diabetes. Dr. Soskin

and I<sup>9</sup> have taken a number of patients into the Max Pam Metabolism Unit of the Michael Reese Hospital and have studied the effect of isocaloric diets varying widely in the proportions of protein, fat and carbohydrate. We have found that from a metabolic point of view there is surprisingly little difference in the results.

Our experiments, therefore, show that a wide latitude may be allowed in treatment. We have found no evidence either in the literature or in practice which would convince us that it is necessary to adhere to one formal method of starting treatment, provided we follow certain definite fundamental rules in the management of all diabetic patients. Certainly in the beginning the most important factor in diet is that the diet be less than enough to meet the full caloric requirements of the patient. Newburgh's low-calorie, comparatively high fat regimen forms a simple nutritional procedure which we frequently employ, usually with excellent results. It is particularly valuable when we aim to make the urine sugar-free quickly. However, if we feel from our initial survey that the patient is not severely ill, then almost any proportion of protein, fat, and carbohydrate may be employed provided that the total diet contains fewer calories than are actually needed to maintain energy balance and that it does not contain an overwhelming amount of fat. Regardless of what the starting diet may be, a few days' observation of the patient's clinical condition and of the amount of his blood sugar and urine sugar will give us a definite indication for further treatment.

For example, the patient is put on a diet of protein 50, fat 100, carbohydrate 50, and in two days his urine is normal. At this point the old fashioned method of gradually stepping up the diet may be followed with safety until a maintenance level is reached. If, however, it is found that with such a moderate diet the patient continues to excrete sugar then we must proceed to determine his carbohydrate tolerance.

This is not difficult. The factors we need to know are these:

- (1) the amount of protein, fat, and carbohydrate in the diet,
- (2) the amount of glucose excreted,
- (3) that every gram of protein utilized yields 58 per cent. of carbohydrate.



On the diet of protein 50, fat 100, and carbohydrate 50, it is evident that the available glucose amounts to 100 per cent. of the carbohydrate, i.e. 50, plus 58 per cent. of the 50 grams of protein, i.e. 29, giving a total of 79 grams available glucose. Let us assume that after two or three days on the above diet the patient is excreting 35 grams glucose. Since his intake was 79 he burned the difference between his intake and his excretion, or 44 grams glucose.

We must now plan to give this patient, who can utilize 44 grams carbohydrate, enough food for him to continue his life's activities and yet remain sugar-free. The weight of the patient, let us assume, is 64 kilograms, or 140 pounds, and his occupation that of chauffeur. The basal need of most men at rest is approximately 30 calories per kilogram of body weight. Therefore, this patient requires 1920 calories, to which must be added at least from 20 to 30 per cent. of this amount for the expense of energy involved in his occupation. This means that the patient should receive approximately 2400 calories, although there is no absolutely accurate standard of caloric needs. Any individual must receive enough protein in his diet to maintain nitrogen equilibrium; the amount varies between  $\frac{2}{3}$  and 1 gram of protein per kilogram of body weight. In our case, if we adopt a minimum of  $\frac{2}{3}$  grams, he would need 45 grams protein. It has already been stated that 58 per cent. of all the protein is utilizable as glucose, so that the 45 grams of protein which this patient is to get is equivalent to 26 grams of glucose. Since his total tolerance is only 44 grams it is at once obvious that his diet can contain only 18 grams carbohydrate if he is to remain sugar-free, and that it is practically impossible to furnish anything like a normal diet of 2400 calories with such a low carbohydrate value. Either insulin must be used or we must readjust his diet in abnormal proportions. The latter will be exceedingly difficult if not impossible, especially if the patient is to remain on the diet for years.

#### INSULIN

It now becomes necessary to give insulin but before beginning we must know certain fundamental principles regarding the use of insulin. We take it as axiomatic that the average patient who is to receive insulin should receive enough to allow him to take a diet with a normal proportion of foodstuffs and with sufficient calories to

permit his usual activities. There is nothing to be gained (except from the standpoint of cost) by setting a limit to the amount of insulin to be used.

There are certain important facts regarding insulin dosage which also must be understood. It is impossible to say that a unit of insulin will be equivalent to a certain fixed amount of glucose. Insulin has not even an "average" value. If one defines the term "insulin coefficient" in the form of an equation

$$\frac{\text{number of grams of glucose utilized}}{\text{units of insulin}} \text{ it will be found to vary greatly.}$$

Dr. Soskin and I, in the experiments already referred to, have shown that in the same patient on isocaloric diets with a respective glucose value of 321, 82, and 169 the insulin coefficient was 10.6, 4.8, and 5.1. This means that in any given case the insulin coefficient must be determined roughly by the method of trial and error. To begin with it is safe to assume a value of 2.5 Gm. of glucose for each unit of insulin used, but constant observation is necessary to revise this figure during the course of treatment. It is a common experience that after acute insults to the metabolism, such as following infections or acidosis, the insulin coefficient is lowered greatly, and as improvement in the clinical condition continues much less insulin becomes necessary for the same amount of glucose.

Certain further details of insulin therapy should be understood in order to obtain the best results. It may not seem necessary to urge the need of examining separate specimens of urine instead of the twenty-four hour specimen. It is impossible to render the twenty-four hour specimen sugar-free in certain patients treated with insulin even though the intake of carbohydrate is diminished or the insulin increased. The analysis of separate specimens voided throughout the day will clearly indicate when this sugar is being excreted. It may be found present only at one time during the day, frequently only in the morning specimen. When found during the day a readjustment of the time relation between meals and the giving of insulin becomes necessary. If sugar is found only in the early morning specimen it is obvious that the insulin given in the evening is not sufficient to render the night urine sugar-free. Under these circumstances we must give insulin at some time during the night if we wish to make the twenty-four hour specimen of urine sugar-free.

Is it necessary to render the blood sugar of the insulin treated patient normal? Again certain details should be known. In the pre-insulin days the starvation blood sugar usually indicated the lowest blood sugar level of the twenty-four hours, and as such it gave a fairly accurate index of the results of treatment. In the insulin treated patient, however, the blood sugar will vary throughout the day according to when insulin is given, and the highest blood sugar level will be in the early morning before breakfast. This will give a false idea of the results of treatment, and the effort to render this morning blood sugar normal seems to me to be unnecessary.

Understanding these principles and details of treatment, we may now begin to treat the chauffeur, who requires 2400 calories and has a tolerance of 44 Gm. of glucose. There is no need for accurate figuring. It is often wise to discuss with the patient the kind of food he likes, and if possible to arrange his diet to suit his taste. It makes very little difference exactly what proportion of foodstuffs is given. His total available glucose is known, and insulin is given in sufficient quantities to cover what is added in the diet. It is our firm belief that the diet should contain sufficient calories to permit the patient to carry on his job, that the distribution of foodstuffs should be as nearly normal as possible, and that in addition the diet should be one which the patient will be willing to adhere to for long periods of time.

These rather broad statements must not be interpreted to mean that the patient may take an unlimited supply of food, or that the patient is to be the sole arbiter of his diet. We have been much interested in estimating the general run of diets of patients treated with insulin to find, rather to our surprise, that they are satisfied with a carbohydrate value somewhere between 125 and 175 Gm. With this amount of carbohydrate it is very easy to construct a nearly normal diet. The protein content may vary considerably. The amount of protein in the American dietary normally has a wide range, depending to a great extent on geographic and social factors. All that remains is fat, which can be ordered to supply the necessary calories. Attention should be directed to the advisability of maintaining the patient either at a normal or slightly subnormal weight, and to warn against overindulgence in food to the point of gaining beyond the normal weight.

The amount of insulin to be given cannot be considered on an

absolute standard. We should know the amount of available glucose in the diet, and as we already know the tolerance to be 44 Gm. it is easy to figure how much glucose must be taken care of by insulin. As a starting point it is perhaps wise to consider that one unit of insulin will "take care of" 2.5 to 3 Gm. of glucose, and it is also wise at the beginning of treatment to administer the insulin three times a day. The amount of insulin figured in this rough way will vary in individual patients and in the same patient from time to time, as we have already mentioned. However, if the details of therapy are carefully watched the exact arrangement of diet and insulin will follow without great difficulty. As soon as seems possible the midday dosage of insulin should be discontinued so that the patient will have to take only two injections instead of three.

#### CLINICAL OBSERVATIONS

One recent case offers an excellent illustration of the changes in insulin requirements so often seen during the course of treatment. It also incidentally illustrates the difference between continued therapy with a high fat diet and one with a normal diet and insulin. The patient was a boy of twenty years who came to our office with the story of the onset of diabetes one year before. There was marked loss of weight and the usual classical symptoms. During the previous year he had been on a high fat diet and had had far from a happy time. He was a student, and found it exceedingly difficult to carry on his studies. He was nervous, had palpitation, and some shortness of breath. During the previous two weeks he had evidently gradually developed acidosis. The examination in our office showed a typical picture of rather severe acidosis, the urine containing a tremendous amount of sugar and acetone, some albumin, many hyaline and granular casts. He was immediately sent into the hospital, and the usual spectacular recovery from the acidosis promptly followed. He left the hospital on a diet of protein 75, fat 125, and carbohydrate 155, taking insulin 50-0-20, and he remained sugar-free and in excellent health. Further data on his insulin dosage are interesting. He had been able gradually to cut his insulin to 30-0-15, slightly more than one-half the requirement when discharged from the hospital, all the while remaining sugar-free. This was in August 1932. Shortly after his autumnal hay fever started making it necessary to increase the insulin to 40-0-25.

However, after the hay fever season was passed he only required 25-0-15, and he remained sugar-free on 40 units a day from October 1, 1932 to April 1, 1933. At this time a mild attack of grippe and some dental infection again made it necessary to raise the insulin to 40-0-30 with a quick drop down to 35-0-20 at the present time.

I can think of no better illustration of the now well-established fact that in an insulin treated patient the insulin requirements are apt to diminish rather than increase during the course of time.

A story such as this illustrates how difficult it would be to treat a diabetic patient completely on the basis of his chemical equation. We have found that when the need for basic chemistry arises it is necessary completely to individualize the work. For instance, if a given patient does not respond according to the generally accepted standards we must make a most intimate inquiry into what is wrong with this patient's metabolism. We may find an unsuspected change in the basal energy requirements, as would be demonstrated by too high or too low a metabolic rate. If at the time of our treatment the patient has a basal metabolism of plus 40 per cent. it is obvious that our estimates of his fundamental caloric needs will be entirely wrong. This patient would be undernourished on an intake supposed to be sufficient to maintain him in equilibrium; he might even be destroying body protein and be producing sugar from protein.

Whenever as a result of the disease or of the treatment given for the disease there is a disturbance of nitrogen equilibrium no calculations are of value unless they include a study of the protein metabolism. As Woodyatt has pointed out, the question of fuel does not depend entirely on what is fed the patient but also on what is burned by the patient. Therefore, the presence of a negative nitrogen balance, meaning destruction of the body protein immediately indicates extra fuel from the patient's own body protein. This naturally must be considered in arranging the diet.

An example of such an instance came to our attention not long ago. A man known to be a severe diabetic precipitated acidosis by overindulgence in alcohol. He was brought out of his acidosis without difficulty by the usually accepted procedures, but on the second or third day he suddenly showed a large amount of sugar in his urine and a return of acetonuria. A study of this patient revealed that some time previously he had had a basal metabolic rate of plus 50 per cent. An immediate determination of the nitrogen

balance showed us an unsuspected and rather large nitrogen loss. It was apparent that our calculations in this instance had to include his endogenous metabolism and we had to consider his basal needs as 150 per cent. of the usual for a man of his height, age, and occupation. A new diet constructed on this basis contained a much larger amount of food and without any increase in insulin he was soon made sugar-free.

### COMPLICATIONS

A few words should be said about the treatment of some of the commoner complications of diabetes. These complications may be divided into those due to the disease and those incidental to the disease. The most important diabetic complications are gangrene and trophic disturbances of the extremities due to impairment of the circulation, eye changes, and the large array of arteriosclerotic manifestations which are now becoming more and more important. A full discussion of this subject would take us beyond the scope of this paper, but I believe that the general indications for therapy can be elucidated in a few sentences.

Take for example surgery on the diabetic. It is apparent that all surgical patients can be divided into those requiring an immediate operation, e.g. those with acute appendicitis, and those whom the physician has time to prepare for operation. It is generally accepted that as soon as such an acute episode as appendicitis is diagnosed there should be no delay in operating, the condition must be handled as an emergency. The preliminary treatment of the diabetes depends entirely on the status of the patient. The presence of glycosuria and acetonuria certainly indicates the use of insulin, although in not very big doses before operation. The anesthetic must be carefully chosen, the operation done with all haste and care, and the postoperative condition carefully watched. A period of temporary starvation rarely harms a diabetic patient, and it is our general policy carefully to watch such a patient, study his urine at two hour intervals, and treat as indications arise. In this connection it is particularly important to guard against dehydration both before and after operation, and for this reason saline injections are employed. If after operation nothing more happens than the expected postoperative glycosuria, very little need be done. If, however, acidosis or persistent glycosuria are noted insulin must be used. When large doses of insulin

are being used it is perhaps safer to give glucose intravenously or by hypodermoclysis.

When there is no urgency time should be taken to prepare the patient for operation. Almost any diabetic patient can be put into the metabolic condition in which he is burning carbohydrate and his urine is free from sugar and acetone. When this condition is attained the patient is temporarily a normal subject for operation. It has been our practice to have such a patient operated upon early in the morning and to give no insulin the morning of the operation. The postoperative treatment already outlined is very carefully adhered to. It is our impression that over-treatment is just as harmful as under-treatment, and that careful watching and treatment according to specific indications achieves the best results.

The complications attendant on arteriosclerosis are now occupying the center of the stage in diabetic therapy. We have been particularly interested in the myocardial changes which often follow arteriosclerosis in the diabetic, especially from the standpoint of therapy. Evidence has gradually been accumulating to indicate that the elderly diabetic, with myocardial changes, should not receive the same type of intense therapy as the younger diabetic. Some experiments performed at the Max Pam Metabolism Unit<sup>10</sup> show pretty clearly that over-treatment of this group of patients has definitely deleterious effects. It is not merely a question of giving insulin, for the amount of carbohydrate available to the heart muscle seems to be the final factor in deciding the treatment. These experiments support the clinical observation that these patients do not react well to severe treatment, and explain why so many of them refuse to follow such treatment.

The question of diabetic coma has been so thoroughly discussed in a recent article from the Clinic of Dr. E. P. Joslin<sup>11</sup> that we need say nothing about it here.

#### SUMMARY

The ultimate aim of treatment of the diabetic patient is the restoration to economic efficiency. Glycosuria and ketonuria must of course be eliminated. Whether or not the patient receives insulin the diet should be one which he can follow in his daily life. Comparatively simple procedures have been described whereby the diet







of the patient may be maintained at his caloric needs. It is our firm belief that the nearer this diet approaches to a normal distribution of food the more likely it is to succeed in maintaining the patient in good health.

### DIABETIC DIET

**SOUPS:** All stock soups and bouillions. Cream soups without flour.

**MEATS:** Meats, poultry and fish of all kinds not prepared with flour. Oysters, clams, lobster, crab, caviar.

**VEGETABLES:** Asparagus, artichokes, cauliflower, cabbage, Brussels sprouts, sauerkraut, onions, young green beans, tomatoes, celery, lettuce, chicory, watercress, spinach, radishes, pickles, olives, mushrooms, egg plant, Swiss chard, either leaves or stalks. Gooseberries.

**NUTS:** All kinds except chestnuts.

**EGGS:** One or two a day.

**DESSERTS:** Gelatin sweetened with saccharin and flavored with coffee, cream or nuts. Ice cream and custards made of cream and sweetened with saccharin or glycerin. One-half grapefruit or one orange.

**BEVERAGES:** Tea, coffee, lemonade sweetened with saccharin or glycerin.

**FATS:** In form of butter, oil, cream, bacon, should be used in cooking, salad dressings, etc.

**CHEESE:** All cheeses.

**BREAD:** ———

**POTATOES:** ———

**FRUIT:** ———

Take nothing except what is on this list. Ask about other things before you take them.

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## HYDROGYMNASTICS

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WHEN I received the invitation from the Chairman of your Committee to present to this meeting the subject of Hydrogymnastics, I consulted the dictionary in an effort to discover the meaning of the word, for I had never heard or seen it before. My search was unavailing, and I was forced to the conclusion that a new word had been coined, and a very good one too.

The dictionary defines gymnastics as exercises in a gymnasium, therefore hydrogymnastics may be defined as exercises in a water gymnasium.

The original water gymnasium was undoubtedly the "ole swimmin' hole," varying in size from the ocean and lake, pond and river, to a still pool in a small stream, and these natural gymnasia, supplemented by a multitude of artificial swimming pools, remain today a source of exercise in water, which cannot be surpassed in many respects for the normal individual.

However, I assume that the object of this demonstration is to show what can be done in the way of exercises in the water for individuals whose muscle groups are more or less weakened by disease, especially poliomyelitis, and therefore I will confine myself to this phase of the subject.

The simplest and most inexpensive form of water gymnasium is the ordinary house bath-tub where many under water exercises may be successfully given to small children. For larger children and adults, especially built tubs and tanks may be used for individual cases, but with both of these the scope of the exercises which can be given is necessarily limited. To serve the real purpose of a water gymnasium a pool equipped with various kinds of apparatus is necessary. The size of the pool will depend upon the number of people to be served at any one time; the money which is available for the cost of construction and operation, which includes the cost

of water and heating of the same. At Warm Springs, Georgia, where we have an unlimited supply of naturally heated warm water there are two large exercise pools, one for use in warm weather and the other, glass covered and heated, to be used in cold weather and on rainy days.

The outdoor exercise pool is 27 ft. x 75 ft. and the winter pool is 35 ft. x 82 ft., and between the two pools is the play pool, which is used for sports, such as water polo, and by those patients who have become expert swimmers, which is approximately 66 ft. square. Pools of this size are necessary there since frequently between 80 and 100 patients are receiving their exercises during the three or three and a half hours of the morning. These pools are built of cement and are very plain in appearance, but have stood the test of years and will probably last for many years to come. Many of the pools which have been built in the past for exercise or gymnasium purposes have been too costly and seem to have been constructed with the idea of impressing visitors rather than of their usefulness to patients.

A cement pool, if it has a smooth finish surface, is really better for exercise work than one with a glazed tile surface, and much less expensive. Also, many of the pools I have seen have been designed by architects skilled in the construction of swimming pools for clubs, and like these pools have been built with sloping bottoms. This is a mistake, for pools that are to be used for exercises, especially those of small size, need a considerable part of the floor to be level, in order that the necessary apparatus may be used to advantage.

Water in the pools should be of a uniform depth, and we found at Warm Springs that a depth of 4 ft. 6 in. was most useful for all cases. If for any reason it seems desirable to have a shallow portion of the pool for small children, it is better to have a series of broad steps rather than a slope.

The most important apparatus for an under water gymnasium consists of a table or tables 6 feet long, 25 inches wide, and made of cypress wood which is not affected by being under water. These tables should have a raised head-rest at one end 21 in. long and 10 in. high sloping to the table top. They should be bolted to the bottom of the pool or if economy of space is necessary, they may be weighted and then lifted out of the pool when other exercises than those on

the table are being carried on. The top of the table should be about 15 in. below the surface of the water.

A heavy chair with an adjustable seat is desirable for arm and shoulder exercises. Bars parallel to the sides of the pool and extending out from the side about 4 in. with the top of the bar just under the surface of the water are useful, especially for exercises of the trunk muscles. Swinging rings and parallel bars for walking in the water are parts of standard equipment, and other forms of apparatus for special cases may be devised as the occasion arises.

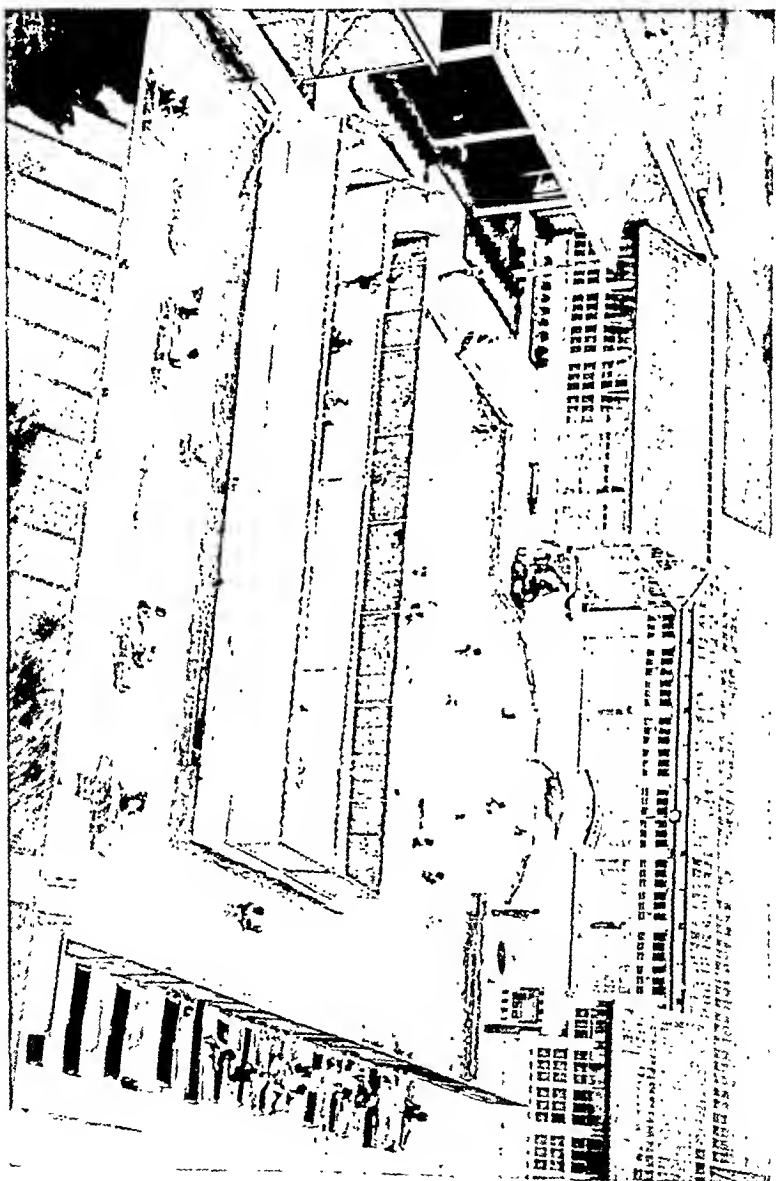
Of course, as in the ordinary gymnasium showers and dressing rooms should be provided, and these will have to be of special construction to meet the conditions present in these patients who have weakened muscles.

Indoor pools may be either sunk or raised from the floor, and probably the latter is, as a rule, more useful for this kind of pool. If the top of the pool is just about the height of the ordinary wheel stretcher the patients can be placed in the pool quite easily and with less effort than when it is necessary to take them down a series of steps.

The temperature of the water should be between 85° and 90°. I have found that in many of the indoor pools the tendency has been to raise the temperature of the water to about 94°, and to have the air temperature 80° or above. I believe that this temperature is too warm for both, and is too exhausting and depressing both to the patients and to those who are giving the exercises.

If the question of equipment or the personnel is a factor, the decision should always be given in favor of the personnel. Properly trained and efficient physiotherapists will be able to obtain very good results with a simple equipment, while no matter how elaborate and complete the equipment may be, if those who are using it have not had the right kind of training the results will not be satisfactory. The technique of exercises in water differs considerably from the exercises given outside, and therefore requires special training. As in the ordinary gymnasium, those who are to have the exercises require a complete physical examination to determine whether they are able to perform the necessary work, and also to endure a water immersion. The exercises for these patients who have been weakened by a disease such as poliomyelitis may be just as strenuous and

FIG. 1.



Patients' Pools at Warm Springs, Georgia, used as an Underwater Gymnasium.



dangerous as the more violent exercises on the apparatus in a gymnasium for apparently normal people.

In addition to the general physical examination, there should be a complete muscle examination with a grading of the different muscle groups, which gradings are entered upon a chart and a copy of this chart should be given to the physiotherapist in order that she may be able to determine how much power each muscle group has and how much resistance can be used.

I wish to emphasize the fact that these exercises are not simply passive movements, but they are to be especially directed and require the same sort of concentration on the part of the patient as gymnasium exercises by the trained athlete.

The length of time during which the exercises should be given to the individual patient depends upon many circumstances, and no absolute limit as to the time or number of exercises can be stated. The criterion is fatigue, and in doing the exercises for any set of muscles the last movement should be done as well as the first. On the average, the exercises for the different groups can be given for ten times, but frequently it will be necessary to stop short of this. The exercises should be given very slowly with an appreciable interval of rest between each, and muscle groups performing opposite motions should not be exercised at the same time. For example, if the extensors are being exercised the movement of the flexors should be passive and controlled by the physiotherapist.

If a muscle or muscle group has very little power, the physiotherapist should assist in the movement and carry the part controlled through a complete arc. When a muscle group grades fair or better resistance should be given to varying degrees, depending upon the muscle power. For these reasons it is important that the physiotherapist be perfectly familiar with the gradings in order that changes in the exercises may be made if necessary.



markedly increased, while in others it may be flattened. If the condition is very painful, there is likely to be a forward and lateral tilt of the trunk with marked spasm of the back muscles. This attitude is a protective mechanism restricting motion at the lumbosacral joint. Of the objective findings the lumbar groove is the only one which is not found in other lesions of the lumbar spine, and it may, therefore, be considered pathognomonic, or at least strongly suggestive of a forward displacement of one of the lumbar vertebrae.

An absolute diagnosis of spondylolisthesis depends upon the roentgen ray findings. Normally the lateral view of the lumbar spine shows a series of quadrangular bodies, the lumbar vertebrae, superimposed on the triangular sacrum (Fig. 2). There is a mild forward curve of the lumbar region. The anterior borders of the bodies of the lumbar vertebrae and the sacrum make an uninterrupted curve, as do also the posterior borders of the lumbar vertebrae and the sacrum. When one of the lumbar vertebrae is displaced forward the line of the lumbosacral curve is broken and the body of the displaced vertebra is seen to be in advance of that of the body below it. For instance, in a displacement of the fifth lumbar vertebra, the body of the fifth lumbar vertebra is definitely in front of that of the first sacral segment (Fig. 3). In the anteroposterior view in a normal spine it is noted that the lumbar vertebrae appear as quadrilateral segments above the sacrum with distinct intervertebral spaces (Fig. 4). When the fifth lumbar vertebra is displaced forward there is also a downward displacement, so that in an anteroposterior view centered over the lumbosacral joint one is looking not at the anterior surface of the vertebra, but at its superior surface which is overlapping the first sacral segment by reason of the forward descent of the dislocated vertebra. Consequently, the anteroposterior view in spondylolisthesis shows the normal quadrilateral outlines of the lumbar vertebrae above the displaced one, while the dislocated vertebra appears as a crescentic shadow lying in front of the sacrum. For over ten years I have believed this to be pathognomonic of spondylolisthesis. In Fig. 5 this particular finding is shown clearly. The second, third and fourth lumbar vertebrae appear as quadrilateral bodies. Below these is seen the outline of the superior surface of the fifth lumbar vertebra, including the crescentic outline of the body anteriorly and posteriorly, the triangular opening of the neural canal, the posterior arch, with the spinous processes in the median

FIG. 1.



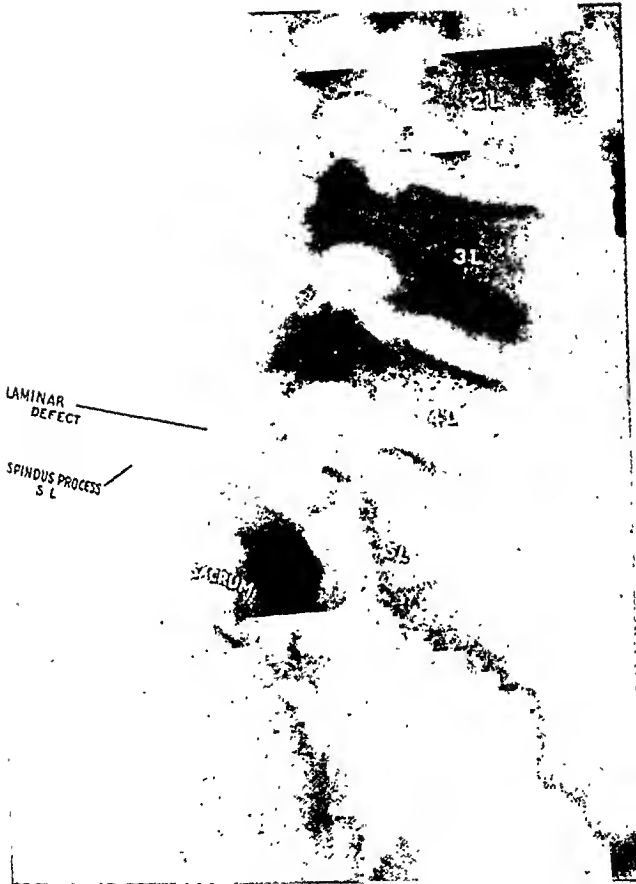
Spondylolisthesis. Shows lumbar groove directly above sacrum.

FIG. 2.



Lateral view of normal lumbar spine. Note quadrangular lumbar vertebral bodies superimposed on triangular sacrum. Note that the anterior borders and the posterior borders of the lumbar vertebrae and the sacrum form continuous uninterrupted curves.

FIG. 3.



Spondylolisthesis. Marked anterior displacement of the body of the fifth lumbar vertebra. Body of the fifth lumbar vertebra is triangular and is displaced forward and downward a distance of at least three-quarters of an inch. There is a marked laminar defect in the posterior arch of the fifth lumbar vertebra. The superior surface of the sacrum is convex. The bodies of the second, third, and fourth lumbar vertebrae are in line with that of the fifth. Compare with Fig. 2.

FIG. 4.



Anteroposterior view of a normal lumbar spine. Note the quadrangular vertebral bodies with distinct intervertebral spaces. The body of the fifth lumbar vertebra is above the sacrum.

FIG. 5



Spondylolisthesis. Anteroposterior view showing displacement of the fifth lumbar vertebra. Note in the upper portion of the sacrum a crescentic shadow representing the body of the displaced fifth lumbar vertebra. The neural foramen of the fifth lumbar vertebra is particularly well seen in (a). (b) represents the spinous process of the first sacral segment. Compare with Fig. 4.



line, and the lateral masses on either side of the neural arch. This shadow lies over the front of the upper part of the sacrum.

#### ASYMPTOMATIC SPONDYLOLISTHESIS

For a long time the students of spondylolisthesis have known that the symptomatology varies greatly in degree. Some patients suffer but little inconvenience, while others are seriously disabled. Not until recently, however, was it appreciated that some people with spondylolisthesis have no symptoms whatever. We are not yet in a position to explain the absence of symptoms in this type of lesion, but it is well established now that there are instances in which there appears to be an almost complete dislocation of a lumbar vertebra without any subjective symptoms or interference with the ordinary functions of the back. In an article about to be published I show roentgen ray pictures of two cases of marked dislocation of the last lumbar vertebra, one in a man fifty-five years old, and the other in an individual of seventy, neither of whom has ever had any back disability.

#### ETIOLOGY

When spondylolisthesis was originally described, it was suggested that the lesion was the result of a congenital malformation of the fifth lumbar vertebra. The lesion was assumed to be the result of a congenital cleft in the neural arch. Somewhat later in the history of this condition, which was observed chiefly by obstetricians, the dislocation was thought to be the result of a malformation, elongation and an attenuation of the laminae of the affected vertebra, permitting forward displacement of this body. Dr. Edgar in his textbook on obstetrics promulgated such a theory of the etiology of spondylolisthesis. This was apparently confirmed by other observers and was thought to be a factor in a fair percentage of cases of spondylolisthesis. When, in recent years, the subject was studied intensively and on a large scale it was found that this lesion occurred in men just as often as in women, and frequently the symptoms appeared after an injury. The opinion then arose that the defect noted in the posterior arch was a fracture caused by the injury.

There were thus three theories to explain this lesion. The theory of *attenuation of the laminae* was subscribed to by but a few observers. I myself at one time had several cases in which I thought



there was an attenuation and an elongation of the laminae, and in fact reported several such cases. Later studies, however, with more accurate roentgenography disproved this opinion and established the existence of a defect in the laminae and a definite solution of continuity in the posterior arch. Dr. Theodore Willis of Cleveland, who has examined over 1500 spines and found some seventy-nine cases of spondylolisthesis, has not found one instance of an elongation of the laminae as a possible cause for spondylolisthesis.

*Trauma* as a cause has been assumed rather than proved. Although in my own experience trauma has been an important factor in about 50 per cent. of the cases, in no single instance has the trauma appeared to be of sufficient force to cause a fracture. Furthermore, none of the roentgen ray pictures have ever revealed any callus. In addition, in the cases which I have operated upon I have not found any callus or irregularity of bone to suggest a fracture. Finally, no observer has ever given proof of the presence of callus indicative of a fracture, while Dr. Willis, in his extensive series has not only found no callus, but has found fibrous tissue uniting the posterior arch to the body in a manner similar to that seen in other congenital lesions. While, therefore, trauma is an important factor in spondylolisthesis, I do not believe that it causes a fracture of the posterior arch leading to a displacement of the body.

The theory of the *congenital origin of spondylolisthesis*, first promulgated when the lesion was discovered, has in recent years been confirmed over and over again by many observers. It is agreed now that there are numerous congenital variations in the conformation and structure of the fifth lumbar vertebra. That this is so may be decided from the statement of the famous anatomist, Thomas Dwight, who said that he could not describe a normal fifth lumbar vertebra because it has so many variations. All of us know how frequently there is a spina bifida occulta in the fifth lumbar vertebra as a result of non union of the two sides of the posterior arch. Many observers, including Dr. Willis, Dr. Chandler, Dr. Turner and others in this country and abroad have found that there is frequently a defect and loss of continuity of the bone at the pedicle separating the superior from the inferior articular processes. The pedicle is the frequent site of the laminar defect resulting in a separation of the posterior arch from the vertebral body. Anatomical specimens prepared by Drs. Willis and Chandler amply demonstrate this fact. I

will show you today roentgenograms also clearly demonstrating the laminar defect. The laminar defect can be explained embryologically on the following basis: A vertebra is formed from five centers of ossification, one for the body and two for each lateral mass. Of the two for each lateral mass one goes to form the superior articular process and the other the inferior articular process and the lamina in back of it. When there is a failure of the two lateral centers of ossification to unite, a defect naturally results in the pedicle. This defect is bridged over by fibrous tissue which connects the posterior arch with the body. In the accompanying illustrations you will note varying degrees or dislocation of the lumbar vertebrae, with the laminar defect distinctly visible.

In the genesis of spondylolisthesis there are several exceedingly important contributory factors. Of these trauma is the most important and the most frequent. Trauma, appearing either as a single force or occurring in milder form but repeatedly, as in severe sports or laborious work, stretches or may actually tear the fibrous tissue bridging the laminar defect, making it possible for the superincumbent weight to displace the vertebral body forward. In a like manner an excessive lumbar lordosis, by increasing the lumbosacral angle, places the fifth lumbar vertebra at an enormous mechanical disadvantage, in that the lumbosacral plane is vertical or nearly so, and aids the force of gravity to displace the fifth lumbar downward from the sacrum. In an exactly similar manner overweight, by increasing the strain at the lumbosacral junction, may stretch and tear the fibrous tissue holding the laminae to the body and cause a spondylolisthesis.

Spondylolisthesis is seen with about equal frequency in both sexes. Some statistics show a slight predominance of females over males, while others show the exact opposite. I, myself, have seen a slightly greater percentage in males than in females. The third and fourth decades of the life span contribute more cases of spondylolisthesis than any other. But this lesion is seen at all ages, except that so far no case has been seen, or at least recorded, in the first decade.

#### PATHOLOGY

The pathology of spondylolisthesis includes all of the objective findings, namely, a lumbar groove, a prominent sacrum, an increase

in the lumbosacral angle, a change in the axis of the sacrum, a forward displacement of the body of the affected vertebra, and a bilateral break in the continuity of the neural arch.

#### PRESPONDYLOLISTHESIS

As may be surmised from a consideration of the pathology, and more particularly the etiology, of spondylolisthesis, there must be a period when, although the essential for a dislocation, namely, a bilateral laminar defect is present, no displacement has yet taken place. Some years ago Dr. Armitage Whitman suggested that there was a stage of prespondylolisthesis, characterized by backache and a moderate lordosis. From what I have already stated, it will be more natural to assume that a prespondylolisthesis is a condition in which there is present the specific laminar defect but without dislocation of the vertebral body. Three such cases have come under my observation, and have been reported in a recent article. In all three cases there were symptoms of backache. In two of these the laminar defect was visible in the roentgen ray pictures. In two cases operated upon a separate neural arch and a bilateral laminar defect were clearly demonstrated. These cases of prespondylolisthesis indicate to us a new avenue for investigation. In those suffering from backache a more accurate study clinically and roentgenographically may reveal a laminar defect indicating the existence of a prespondylolisthesis or an incipient spondylolisthesis. Arrest of the process of dislocation and prevention of future disability may be obtained by a stabilization of the back through a spine fusion.

#### TREATMENT

The treatment of a case of spondylolisthesis depends to a large extent upon the subjective symptoms. If these are mild, conservative treatment may be resorted to. This would consist of a support to the back by means of some form of corset or brace, and the limitation of activity to non-laborious work. If the symptoms have persisted over a long period of time or, if they are of short duration but severe and cannot be relieved by external support, the condition can be cured by a spine fusion operation. This type of radical treatment has been effective in every one of the cases to which I have applied it.

# THE MANAGEMENT OF ACUTE HEAD INJURIES\*

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THE proper care of patients suffering from acute head injuries depends on one's ability to interpret correctly the changing train of signs and symptoms exhibited and upon an understanding of the underlying pathological changes that may occur in the brain and skull as a result of injury. It should be emphasized that it is the damage to the brain and not the actual fracture of the skull which is of importance. Thus there may be only a small linear fracture, but such severe damage to the brain that a fatal outcome follows; or the roentgen ray may show multiple radiating fractures whereas the patient may exhibit little evidence of actual brain injury.

In analysing large series of cases of head injuries, it is obvious that there are several groups into which they may be divided. In one group the injury is so slight that recovery will surely follow; in another the damage is so severe that death can be predicted with certainty; while in a third group the outcome is problematical. It is in the third group that we have to use all of our diagnostic and therapeutic ability to turn the tide towards recovery.

## DEPRESSED FRACTURES

Three classes of cases require immediate surgical treatment, i.e., operation. They are the cases with depressed fractures, with compound fractures, and with extra or intradural hemorrhage. The diagnosis of depressed fracture may be made in several ways. In the first place, such a fracture should be suspected when the head has been struck with a small blunt or sharp object, such as a hammer, an ice pick, the corner of a brick, the edge of a bumper, etc. When such an object has caused a head injury, roentgen ray examinations should be made at once. The depression may be seen or felt in the bottom of a scalp wound. *Every scalp wound should be explored*

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before it is sutured. Each year in our clinic we see several compound depressed fractures which had been overlooked at the time of suture. Some of these were infected when first seen by us, and their management was most difficult and unsatisfactory. How much better to discover the fracture immediately after the injury when conditions are such that adequate treatment can be instituted. Depressed fractures should be elevated as soon as possible after their occurrence. Delay means more and more permanent damage to the sensitive brain cells beneath the fragments.

#### COMPOUND FRACTURES

Compound fractures should be operated on at the first possible moment. The chief danger of delay is infection. The operative procedure consists in careful and wide débridement of the soft tissues, removal of small loose pieces of bone, elevation of depressed fragments, débridement of dura, irrigation of the damaged brain to wash away the hopelessly damaged cortex, closure of dura (a fascial transplant from the thigh, if necessary), replacement of bone and suture of the scalp without drainage. The operation can be done readily under local anesthesia.

#### EXTRADURAL HEMORRHAGE

It is of vital importance to diagnose an extradural hemorrhage, for in operation alone lies the patient's sole chance of recovery. I feel sure that many persons die each year from unrecognized extradural hemorrhage. The hemorrhage usually occurs from the middle meningeal artery, the blood stripping the dura from the skull as it compresses the brain. It is easy to see how the bleeding within a rigid box (the skull) can cause high degrees of brain compression. The history of an injury to the head with *primary loss of consciousness* lasting a short time, a clear interval with regaining of consciousness, and a *second loss of consciousness* is typical of extradural hemorrhage. The clear interval varies in duration from a few minutes to several hours depending on the rapidity with which the hemorrhage accumulates, which in turn is dependent on the size of the bleeding vessel. The signs and symptoms of extradural hemorrhage other than the typical history are those of increased intracranial

pressure, and, in addition, we have come to lay great stress on a dilated pupil on the side of the lesion and a motor weakness on the opposite side. The treatment is early operation with evacuation of the clot or ligation of the bleeding point.

#### HEAD INJURIES NOT REQUIRING IMMEDIATE SURGICAL TREATMENT

Having disposed of the types of head injury which require immediate surgical intervention, we now come to that infinitely larger group of patients in which the outcome depends largely on the interpretation of the signs and symptoms and upon the institution of the proper therapy, i.e., the group referred to above in which the outcome is problematical. We are concerned particularly with combating the increased intracranial pressure which results from head injuries for when all is said and done, the reduction of a high pressure to a normal one is all that we can hope to accomplish. The repair of intrinsic damage to the brain cells is beyond our control. The evacuation of clots, the care of compound fractures, and the method of treating extradural hemorrhage have been dealt with. If then we are to devote our efforts to the control of increased intracranial pressure, we must be able to recognize it as it occurs. The signs and symptoms of head injuries may be divided into two groups, i.e., those of general increased intracranial pressure, which include headache, vomiting, changes in the state of consciousness and the alterations in the pulse, respiration, temperature, blood pressure, eye-grounds and spinal fluid pressure; and localizing signs most important of which are paralysis, convulsions, pupillary changes and changes in the reflexes.

#### CHANGES IN STATE OF CONSCIOUSNESS

Valuable indications for prognosis and therapy may be learned from the state of consciousness. In a recent study of 389 cases admitted to the Cincinnati General Hospital, 106 were fully conscious on admission with a mortality of 7.2 per cent.; 106 were semi-conscious with a mortality of 16.7 per cent.; while 177 who were deeply unconscious and remained so for varying lengths of time had a mortality of 68 per cent. A returning consciousness or retention of consciousness at the same level, even in the presence of other disquieting symptoms is quite favorable, but a deepening coma is

an indication that the case is progressing unfavorably and measures for relief of pressure should be instituted.

#### TEMPERATURE

The temperature means little when the patient is first seen unless it is extremely high or unduly low—in either event the prognosis is poor. The subsequent curve of the temperature is of great importance. In favorable cases the temperature rarely goes beyond  $102^{\circ}$ , and a steadily mounting fever is of very grave prognostic import. Recovery is rare with a temperature of  $105^{\circ}$  or over. Lacerations of the cortex are accompanied by high fever while edema is said to produce low fever. Meningitis is usually ushered in with a sudden rise in temperature of several degrees.

#### PULSE

Progressive slowing of the pulse means a progressive increase in intracranial pressure and is an indication for the relief of pressure. A steadily mounting pulse is an indication of impending disaster, but a slowly rising pulse that does not go over 90 to 100 is a good sign. When the pulse rate changes from very slow to very rapid in a short space of time the prognosis is utterly bad for this usually means that the stage of cerebral decompensation has been reached.

#### RESPIRATION

In order to form a satisfactory estimate of the character of the respiration, close observation of the chest for several minutes is essential. Otherwise, slight variations which mean so much will be overlooked. A steadily slowing respiration means increasing pressure, while slight periodic irregularity in depth of respiration is of the greatest importance as an early sign of dangerously high pressure. Cheyne-Stokes' respiration is associated with the gravest prognosis. When it occurs in conjunction with a weak, rapid pulse and deep coma, a fatal outcome practically always ensues.

#### BLOOD PRESSURE

It has been our experience that blood pressure changes are not consistent enough to warrant placing much reliance on them as an index of increasing intracranial pressure.

## CHANGES IN THE FUNDUS

Changes in the fundus do not occur early enough to be of aid in the acute stages of the injury when help is most needed. In the later stages with chronically increased intracranial pressure, the examination of the eyegrounds and the finding of a choked disc is of importance.

## SPINAL FLUID PRESSURE

The spinal fluid pressure may be recorded on several types of manometers. We use a vertical manometer graduated in centimeters of water, taking 8-12 cm. as normal. We do not feel that any reading is absolutely correct in so far as it gives an exact measurement of intracranial pressure, but we do feel that fairly definite conclusions can be drawn, even if there is some degree of error. Accurate readings can be obtained if the manometer is not connected until the patient is quiet, if his respiration is unobstructed and if his head is not flexed so as to compress the jugular veins. Unless the patient is comatose, local anesthesia should be used for the puncture. The puncture may be done as frequently as indicated. The manometric readings, except in isolated instances, furnish us with our most accurate index as to what the intracranial pressure actually is, and we have come to rely upon them greatly. However, it should not be the sole criterion for therapy. It is necessary to take into consideration the other signs and symptoms in conjunction with the manometric readings.

## CHANGES IN PUPILS

In the 389 cases referred to above, 119 who had unequal pupils on admission had a mortality of 59 per cent. Two hundred and fifty-nine who showed no pupillary changes had a mortality of 26 per cent. The amount of intracranial damage is rather accurately indicated by changes in the pupils. Where the amount of damage is extreme, both pupils are apt to be dilated. This phenomenon was associated with a 100 per cent. mortality in our series. When a pupil which was dilated, contracts to normal size, the outlook is favorable, but when a pupil which was equal to its mate later becomes dilated, it is an indication that the intracranial damage is progressing and suggests an intradural or extradural hemorrhage.



## PARALYSIS

Hemiplegia is found to be associated most often with extradural hemorrhage, and in our opinion is always an absolute indication for operation. It would seem useless to attempt to treat by spinal puncture a patient with a consistent weakness of one side. One must rule out an apoplectic stroke occurring before the fall which was responsible for the head injury.

## REFLEXES

Reflex changes are rarely found, are apt to be transient and are unreliable. The greatest value that one learns from reflexes is that absent reflexes are of grave prognosis and that any real change in reflexes means more damage within the cranium and therefore a more serious prognosis than if the reflexes were unchanged.

## BLEEDING

Bleeding from the ears, nose, or mouth means extensive damage to the base of the skull, and a resulting high mortality. Negligence in the proper care of bleeding ears may result in otitis media, mastoiditis, and meningitis. We have been in the habit of cleansing the external ear with alcohol, avoiding irrigations or the introduction of packs in the canal and applying securely a copious sterile gauze dressing. This is changed as often as is necessary.

## TREATMENT

As has been mentioned previously, the chief purpose of the treatment of head injuries is to keep the intracranial pressure as far as possible within normal limits. The various methods which have been and are still used to effect this are decompressive operations, spinal punctures and the administration of dehydrating solutions in the hope of decreasing the brain volume. Of these methods we prefer spinal puncture. If the pressure cannot be controlled by repeated punctures, subtemporal decompression should then be done. Recent work tends to show that the dehydrating solutions cause slight or transient reductions in pressure which are apt to be followed by an increase in pressure above the original one.

The proper treatment of head injuries, exclusive of those requir-

ing immediate operation, consists (1) in careful physical and neurological examination, a carefully controlled spinal puncture with record of pressure and character of spinal fluid; (2) a period of observation with fifteen-minute charting of pulse and respiration. During this period of observation one determines by the changing signs and symptoms, supplemented, if necessary, by repeated spinal punctures with record of pressure, the progress of the patient. If the patient is improving and the pressure is decreasing or remains within normal limits, nothing further is done. If the patient does not show signs of improvement and the pressure is increasing or remains high, repeated spinal punctures are done withdrawing *slowly* and *carefully* enough spinal fluid at each puncture to bring the pressure to normal. If, however, in spite of repeated puncture the pressure remains at a dangerously high level, an operative decompression is performed.

Any patient with a real head injury should be kept in bed at least twelve days, preferably two or three weeks. The pressure of the spinal fluid should be normal on discharge from the hospital.

# Clinical Pathology

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## CLINICAL PATHOLOGICAL CONFERENCE\*

### Two Instances of Jaundice

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CASE 1.—B. C. Unit History No. 40584. Admitted December 8, 1931. Died December 10, 1931. A colored woman, thirty-three years of age, was brought to the hospital in a deep stupor. The history of her illness was obtained from the husband and other relatives. She had always been strong and healthy until a year before. She had had a few of the minor diseases of childhood but had never been seriously ill. She had had one child, born dead, ten years before. No other pregnancy. She had always worked steadily and had led a regular life. A year before coming into the hospital she began to have dull pain on the left side of the abdomen. About a month later a small tumor about the size of a nut appeared in the lower part of the abdomen on the left side. This seemed gradually to drop down to the left thigh, a little below Poupart's ligament, where it formed a tumor the size of an egg. The pain in the left side became increasingly worse. Six months before admission this tumor was incised and a small amount of pus was discharged. The swelling recurred and was opened at irregular intervals until two months before coming to the hospital, when suddenly it opened spontaneously and discharged a large amount of pus, estimated at from one to two quarts. Following this there was no further discharge.

A little over a month before coming to the hospital a blood test was made and the patient was told she had bad blood. She received an injection into the arm vein and a second injection three weeks before admission. This second injection was followed by chill, fever, arthralgia and malaise. Apparently the fever continued for some time for the patient became weak and indisposed and two weeks before admission she was obliged to stop her work and go to bed on account of weakness and pain throughout the body. She seemed to be getting better of these symptoms until four days before admission when jaundice was noticed. Two days later she began to talk incoherently, became delirious and then passed into stupor. During the six weeks of illness the patient had gradually lost weight.

*Examination.*—Temperature, 97.8°; pulse, 100; respirations, 24; blood pressure, systolic 148 mm. Hg, diastolic 90 mm. Hg.

A well-developed, well-nourished Negress, showing the evidence of only a little loss of weight. She was in a deep stupor but when aroused became maniacal and combative, uttering wild shrieks. Marked jaundice. Pupils were equal, left irregular, both reacted to light. Eyegrounds showed no abnormality.

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The tongue protruded in the midline and was clean. The teeth were in fair condition. The throat showed nothing remarkable. A few of the superficial lymph glands were palpable but there was no marked glandular enlargement. The chest was symmetrical. The lungs were clear, except for a little dullness in the right interscapular area where the breath sounds were blowing in character. No rales were heard. The heart was not enlarged, sounds were regular and clear. Pulse was regular, equal at the two wrists; vessel walls were not thickened. The abdomen was soft, no rigidity, no masses. Liver flatness extended from the fifth rib to the costal margin. The spleen was not enlarged. No fluid. The spine was straight, no evidence of deformity or tenderness. Possibly a small depression at the tenth dorsal vertebra, with slight fixation of the spine in that area. On the inner aspect of the left thigh, 5 cm. below Poupart's ligament, was the mouth of an old sinus tract. No discharge. Margins of the sinus were indurated. Reflexes were all hyperactive. Knee kicks and ankle jerks on the right side were more active than on the left. Ankle clonus on the right. No Babinski. Negative Kernig. No evidence of loss of muscle power.

*Course in the Hospital.*—The patient was given several intravenous injections of glucose without any improvement in her condition. Pulmonary edema came on, the patient became more and more dyspneic and died on the second day after admission. During the two days she was in the hospital the liver grew smaller. On admission it is stated that dullness extended definitely from the fifth rib to the costal margin. Later the area of liver dullness was extraordinarily small. Those who observed the patient on admission made these second examinations and were convinced that a remarkable change had occurred in the size of the liver. The jaundice grew deeper.

*Laboratory Examinations.*—

*Blood Count:*

Hbg. 63%. Red blood cells, 4,230,000. White blood cells, 18,000.

*Differential*

Polymorphonuclear neutrophils	87%
Lymphocytes	7
Monoocytes	2
Myelocytes	4

*Blood Culture:* No growth.

*Blood Chemistry:*

NPN	Sugar	NaCl	CO <sub>2</sub> Comb. Power	van den Bergh prompt biphasic
32 mg.%	72 mg.%	452 mg.%	24 Vols.%	16 mg.%

*Wassermann Reaction on Blood Serum*—Anticomplementary; flocculation test positive.

*Spinal Puncture:* 3 cells; Pandy negative; Wassermann reaction negative; colloidal mastie test negative; culture: no growth.

*Urine*—A trace of albumin. Large amount of bile; many bile-stained casts. Urine culture: no growth.

*Gastric Contents:* No free hydrochloric acid.

*Roentgen Ray Examination: Chest*—No gross changes in lungs.

*The temperature varied from 97° to 99°.*

*The pulse varied from 100 to 140.*

## DIAGNOSTIC DISCUSSION

There is no difficulty in making a satisfactory diagnosis of the final illness. The characteristic triad of symptoms, deep jaundice, profound intoxication and rapid reduction in the size of the liver, are the typical clinical manifestations of acute yellow atrophy of the liver. Objections are frequently made to this designation and for reasons that are obvious. The disease is usually not very acute, the liver is seldom yellow and the cells do not show atrophy. Necrosis of the liver is a more accurate term. However, acute yellow atrophy, though literally inappropriate, has the sanction of long usage and it is desirable to retain the term for historical reasons if for no other. All we need ask is that it be used to name a disease and not as a correct description of the disease.

Acute yellow atrophy of the liver is one of the rare diseases. Howard<sup>1</sup> in 1927 reviewed the records of the Montreal General Hospital and found only seven instances in 24,944 admissions. But during the past twenty years it has increased in frequency and we encounter it now many times more often than we did thirty or more years ago. For instance Osler<sup>2</sup> found only three cases among 28,000 medical admissions to the Johns Hopkins Hospital, whereas during the past two years four cases have come up for consideration at these conferences alone. It is to this point that we wish especially to call attention for it has an important clinical bearing since the increase is due almost entirely to the extensive use of arsenical preparations in therapeutics, particularly to the use of arsphenamine in the treatment of syphilis. Of the four cases of liver necrosis considered at these conferences during the past two years two were undoubtedly due to arsphenamine and another probably due to it. This is the fifth case and here again, there can be little doubt, arsphenamine is the cause. A month before coming to the hospital the patient received an intravenous injection following a positive blood test. A week later a second injection was given. Following this second injection the patient had a violent reaction and thus began the illness that rapidly led to death.

We cannot here review all of the untoward symptoms that frequently follow the intravenous injection of arsenic. We must restrict our attention solely to its effect upon the liver. From experiments

upon animals and observations upon human beings it is reasonable to assume that full doses of arsphenamine always cause changes in the liver cells. (Barron<sup>3</sup>) Due to the extreme tolerance of the liver towards even repeated insults usually no gross evidence of this injury appears. However, transient jaundice often occurs, occasionally still more severe symptoms of liver damage and now and again a fatal degree of necrosis, as is illustrated by this patient. When we consider the innumerable injections of arsphenamine that are daily given then we must allow that serious accidents happen to only a very small proportion of the patients so treated. Further than this, when we take into account the tremendous benefit that comes from these injections, a benefit that could be obtained in no other way, then we must admit that this benefit far outweighs the harm that is occasionally done. The risk that is run is fully justified by the anticipation of the reward that will follow. Nevertheless although we gladly allow all this still we insist that the danger of the treatment should be realized and all the more because this danger is often ignored. When we are called upon to treat an infection of such serious consequence as syphilis and at the same time bear in mind the danger to which the family and neighbors of the patient are exposed, it would be utter folly to even hesitate to use the potent arsphenamines. But to have recourse to them under circumstances when some other harmless treatment will serve as well, even though the treatment may be more tedious and more time consuming, is inexcusable.

Recent investigation has shown a remarkable relation between the diet and the effects of different poisons upon the liver. Whipple<sup>4</sup> and others have demonstrated that a high carbohydrate, low fat diet greatly reduces the effects of chloroform and other fat soluble poisons. Craven<sup>5</sup> has found that in animals a high carbohydrate, low fat diet intensifies the effects of arsphenamine upon the liver, whereas a high protein diet somewhat diminishes them and a high fat, low carbohydrate diet has a highly protective influence. These established facts may perhaps be of some value to the clinic.

The recognition and identification of arsphenamine injury to the liver may occasionally be difficult owing to the fact that now and again the symptoms of acute yellow atrophy may appear as the result of the action upon the liver of the syphilitic infection itself. This

sometimes occurs during the stage of secondary manifestations. Cases are reported in which the rapidly advancing symptoms of acute yellow atrophy were promptly halted and the patient eventually cured by the intravenous injection of arsphenamine.<sup>6</sup> In such a critical situation when an immediate effect is demanded probably no other treatment would be efficacious and yet how difficult it might be to come to a prompt and just decision. Fortunately the dilemma arises but very, very rarely.

In recent years another popular drug has been added to the list of those producing serious injury to the liver. More than thirty instances are now reported of death from acute or subacute atrophy of the liver following the prolonged use of cinchophen.<sup>7</sup> Since cinchophen is now commonly purchased and taken without the advice of physicians and since it is frequently included in proprietary rheumatism cures, its possible relation to obscure instances of acute yellow atrophy must be remembered.

We now turn our attention to the other interesting clinical manifestation which so far we have ignored, i.e. the abscess in the left groin. A year before the patient came under observation she began to have pain in the left side of the abdomen. A month later a tumor appeared in the left groin below Poupart's ligament. This swelling was incised on several occasions and after each incision discharged a small amount of pus. Finally two months before entering the hospital it ruptured spontaneously, discharged a large quantity of pus, and then promptly healed leaving no evidence of its presence other than the small mouth of a superficial sinus.

Where this abscess arose one cannot say. Its location suggests that it was a psoas abscess and since from the history we are led to believe that the patient did not have the constitutional symptoms that nearly always accompany a pyogenic abscess we suspect that it was a cold or tuberculous abscess. Were it a tuberculous abscess we would then assume that it was secondary to tuberculosis of the vertebrae. Some support for this assumption is found in the note of the physical examination stating that there seemed to be a little depression of the tenth dorsal spine. However, during the few days the patient was under observation she was too ill for those in charge to press investigation of this matter. So all we can say is that the patient had an abscess in the left groin. It may have been a tubercu-

lous abscess secondary to vertebral tuberculous, but of this we cannot be sure.

The only other question we need consider is whether there was any intimate relation between the abscess and the liver disease. In diagnosis it is always important to try to explain all of the clinical symptoms as manifestations of one disease. If we assume that two independent diseases are present we are likely to be wrong; if we assume that three or more are concerned we are almost certain to be wrong. However, under the present circumstances I can see no possible way of bringing together the abscess and the liver necrosis under a single nosological category. Even though the abscess may be tuberculous, tuberculous could not possibly produce the rest of the clinical picture. The final symptoms that preceded death are so characteristically those of arsphenamine poisoning and the evidence that the patient had shortly before received arsphenamine intravenously, though only circumstantial, is still of such a high order of probability that there can be little doubt that death and the symptoms immediately preceding were caused by arsphenamine poisoning and bore no relation to the preexisting lumbar abscess. Therefore, the final clinical diagnosis reads:

Syphilis—(Wassermann test).

Arsphenamine poisoning—acute yellow atrophy of the liver.

Abscess in left groin—tuberculous?

#### THE LESIONS FOUND AT AUTOPSY, AND THEIR RELATION TO THE SIGNS, SYMPTOMS AND CLINICAL DIAGNOSIS

Any proper understanding of diseases involving disturbed liver function must rest upon two important facts. First, the liver is an organ which possesses a very great reserve functional capacity. All organs, of course, possess a considerable amount of functional reserve, and it is obvious that this provision is essential for the survival of any species. Different organs, however, differ in the amount of functional reserve which they possess. The liver is extraordinarily well protected in this manner. Ninety-five per cent. of its substance can be removed from dogs and monkeys without producing jaundice or hepatic insufficiency, and there is ample pathological evidence that only a relatively small fraction of the entire liver substance is



necessary for life in the human being. The second fact of importance is the great regenerative ability of the liver. Organs which not only have an excess of tissue as a reserve but also can rapidly replace destroyed cells by new functioning ones are obviously doubly protected against the effects of injurious agents. It is commonly stated that the capacity for regeneration varies inversely with the degree of specialization of the tissue under consideration. There is, however, really no basis for this popular generalization in the case of higher animals. The regenerative ability of the highly specialized renal epithelium is astonishing, as one repeatedly has the opportunity to observe in those cases of mercury poisoning in which life persists for some days following the destruction of the cells; and in the case of the liver, regeneration to restore lost cells proceeds with great rapidity and ease in spite of the fact that each individual hepatic cell is highly specialized to perform a variety of different functions in carbohydrate, protein, hemoglobin and bile metabolism.

Great reserve power and high capacity for replacement of lost cells by new ones place the liver, therefore, in a peculiarly favorable position in the face of injurious agents. It is because of this that hepatic insufficiency plays so small a rôle in most cases of cirrhosis. It is because of this that the organ can be riddled with necroses during typhoid fever or with tubercles in miliary tuberculosis, or largely replaced by metastases from a malignant tumor without the occurrence of any symptoms of hepatic insufficiency, unless the metastases mechanically obstruct the larger bile ducts. Indeed, if the destruction of the cells proceeds slowly and gradually, the concomitant regeneration renders it almost impossible that a stage of hepatic insufficiency ever be reached. If, however, the destruction of tissue be sudden and widespread, the limit of reserve may be passed, too little functioning tissue may be left to meet the normal demands of the body, and symptoms of hepatic insufficiency may appear. This is the state of affairs in so-called acute yellow atrophy, the term ordinarily applied, because of long usage, to any sudden and widespread destruction of liver tissue. If practically all of the liver cells are destroyed at once a stormy course leads rapidly to death before there is time for the accomplishment of any regeneration of tissue. If the destruction of tissue is less extensive, but nevertheless great enough to make serious inroads upon the func-

tional reserve, symptoms of hepatic insufficiency will appear but a sufficient number of cells may be left intact to preserve life until they are able by their proliferation to regenerate enough tissue to restore hepatic function to normal. The symptoms gradually disappear as more and more tissue is regenerated, complete recovery may take place, and the patient may thereafter carry on his normal activities with no further difficulty. Midway between these extremes are the cases in which the amount of tissue spared by the destructive agent suffices to maintain life for some days in the face of severe hepatic insufficiency; the process of regeneration begins, but death occurs before an amount of tissue sufficient to restore the function has been replaced. As you will see, the present case illustrates very well this latter event.

At autopsy (No. 12312) the tissues of this patient were deeply jaundiced and this, as well as various other signs and symptoms which have been recounted to you, resulted from the widespread destruction of liver tissues which is apparent at a glance at the organ. You see that it is very small—about one-third the size of a normal liver. It weighs only five hundred grams. The capsule is wrinkled, for it is now too large a covering for the shrunken liver substance. The general color is purplish-red, but here and there are irregularly scattered, slightly elevated, little yellow or gray nodules. On section you see that most of the cut surface is purplish-red in color, but here again there are scattered grayish nodules several millimetres in diameter. The purplish-red substance which composes most of the organ represents the portion in which the hepatic cells have been completely destroyed and liquefied. The color is given by the blood in and between the sinusoids, which are concentrated because of the collapse of the framework. The gray nodules are the only areas in which liver cells still persist. The bile ducts are normal and not obstructed, but the gallbladder contained only a small amount of viscid mucus and the contents of the intestines were clay colored.

The only other organs which are grossly abnormal are the kidneys and the lungs. The *kidneys* are striking because of their bright yellow color which plainly indicates the presence of large amounts of lipid in the renal epithelium. Otherwise the architecture is normal. The *lungs* show areas of purplish-red consolidation suggesting the familiar result of terminal aspiration of stomach contents.

The *left groin* was carefully explored. There was found only a rather large area of scar tissue in the subcutaneous layer, which was especially dense in the region of the inguinal lymph nodes. The psoas and other muscles were normal, as were the vertebrae and the hip joint.

We shall now project upon the screen the microscopical sections of the abnormal tissues.

This section you would hardly recognize as *liver* for the normal architecture is everywhere obliterated. You can see the remains of periportal areas marked by the hepatic arteries, portal veins and bile ducts, but we pass field after field in which there is nothing between these isolated periportal areas except sinusoids brought close together by the collapse of the reticulum framework from which the hepatic cells have completely disappeared. Here, however, we come upon small islands of liver cells which have not been destroyed. They are sharply outlined against the collapsed framework about them, and they are for the most part completely isolated from the periportal bile ducts (Frontispiece). In most of the islands the hepatic cells are perfectly well preserved, but it is interesting that here and there are exactly similar sharply outlined little islands in which the liver cells were undergoing destruction at the time of death, or had been destroyed just before death. You see that the outlines of the cells are preserved, but many have lost their nuclei and in others the nuclei are undergoing karyolysis and are fading from view (Frontispiece). Now the areas in which no liver cells remain represent areas in which the destruction occurred some days before, sufficient time having elapsed to permit the liquefaction and complete disappearance of the dead cells. The presence of very freshly necrotic cells such as we have just seen in islands which were spared during that original attack is of interest as evidence that in arsphenamine poisoning of this type there is not simply one single explosive attack on the liver, but that the injurious agent may continue for some days to attack cells which were spared during the first widespread destruction. There is a beginning sprouting of bile ducts, and the irregular arrangement of the cords of hepatic cells in some of the islands of liver tissue indicates that regeneration of these cells was also under way. Had the destruction of tissue been less extensive, leaving an amount of substance sufficient to maintain life, and had there been no complication of pneumonia, these islands of liver tissue would

have grown progressively larger, bile ducts in the periportal areas would have proliferated actively, and cords of liver cells would have fused with the sprouting bile ducts, re-establishing communication between the ducts and the intracellular bile canaliculi with remarkable precision. The production of a sufficient number of liver cells would eventually have permitted the removal of the excess of bile pigment from the circulation and from the tissues (for, of course, the function of the hepatic cell is to excrete, not to manufacture bile pigment) and the jaundice would have disappeared. Concomitantly, the other functions of the liver would likewise have been restored to normal.

In this section of the *kidney* you see that the general architecture is quite normal, but here in a section stained to show lipoid you see that all of the cells of all portions of tubules, with the exception of those of the collecting tubules, are loaded with fat droplets, a condition not uncommon in arsphenamine poisoning. The lipoid is not doubly refractile. There are numerous bile stained casts in the tubules.

Although the *aorta* showed no gross evidence of syphilitic aortitis, this section as you see shows perivascular accumulations of lymphocytes in the adventitia and an occasional minute scar in the media. This was the only evidence of syphilis found in the entire body.

This section of *lung* shows the terminal pneumonia.

Finally, here is a section from the *lesion in the left groin*. It shows merely old scar tissue with a few foci of macrophages laden with fat. The reaction is entirely nonspecific, and both the gross and microscopic appearance of the region suggests the end result of an infection extending from the inguinal lymph nodes (granuloma inguinale?). Indeed, here you see a lymph node almost entirely replaced by connective tissue which is continuous with the surrounding scar tissue.

The important points in the anatomical diagnosis in this case, therefore, are:

- 1) Widespread necrosis of the liver (arsphenamine poisoning).
- 2) Lipoid deposits in renal epithelium.
- 3) Slight syphilitic aortitis.
- 4) Healed infection of left groin.
- 5) Terminal aspiration pneumonia.

We need not dwell at length upon the relation of the clinical signs and symptoms to the lesions found at autopsy, for we are dealing simply with a case in which the various functional activities of the liver have been reduced to a point severely endangering, or perhaps actually incompatible with life. It is impossible to say whether or not the patient would have lived for any appreciable length of time had not pneumonia supervened, but it would seem extremely unlikely. The blood sugar level in such cases may be lowered, just as it is following experimental ablation of the liver (in the present case the recorded level of blood sugar may have been influenced by the therapeutic intravenous injections of glucose); amino-acids are not properly deaminized and tyrosin and leucin appear in the urine; the plasma fibrinogen, which is normally produced by the liver, is diminished and coagulation of the blood may be disturbed by this and by the jaundice which occurs. The jaundice is the result of the fact that there remains too little liver tissue to excrete from the blood the amount of bile pigment produced plus the amount which is removed from the circulation but which, mixed with other biliary constituents, escapes freely from the interrupted canaliculi and is resorbed back into the circulation. This pigment, which has passed through the liver cells, gives a prompt van den Bergh reaction in the plasma and escapes as bilirubin into the urine. The death of liver cells and the interruption of the bile canaliculi prevents the excretion of pigment into the intestine, and the stools are therefore clay colored. This triad—acholic stools, bilirubinuria and prompt van den Bergh reaction—is characteristic of *regurgitation jaundice*, which results from necrosis of liver cells or from obstruction of the bile ducts. In sharp contrast are the findings in cases of *retention jaundice*, which result from an increased production of bile pigment in the face of diminished functional capacity of the liver, and in which the laboratory tests reveal exactly the reverse situation of increased pigment content of the stools, absence of bilirubinuria (but increased urobilinuria) and delayed van den Bergh reaction.<sup>8</sup> Time prevents any more detailed discussion of the very interesting and important problems relating to these various disturbances of hepatic function.

For a time there were those who maintained that when hepatic necrosis occurs following the treatment of syphilis with arsenicals,

the damage is caused not by the drug but by syphilis itself. It is now well established through experiment and clinical observation, however, that salvarsan and the allied arsenicals can themselves cause extensive hepatic necrosis. Slight damage to the liver following treatment is common, as witness the frequency with which the blood bilirubin becomes elevated following the injections without the occurrence of tissue jaundice. Transient jaundice is, itself, not so uncommon; but necrosis of the liver of sufficient extent to cause severe hepatic insufficiency is quite rare indeed when one considers the enormous number of patients treated. The manner in which sudden and widespread hepatic necrosis is brought about is not perfectly clear, but it is known that although these drugs are in part excreted by the liver, they are also stored primarily in the liver cells for a considerable period of time following the injection. Since, as in the present case, necrosis of the liver may occur suddenly after the lapse of several weeks following the injection, it seems likely that, under the influence of some accidental accessory condition which alters the internal metabolism of the liver cells, the arsenic which is harbored within them in an innocuous state becomes converted into a toxic form which kills the cells that contain it. Those cells in which it is either absent or present in low concentration, or else in which the chemical alteration does not occur, are spared. What the conditions may be which are able to bring about this chemical transformation cannot be defined precisely at present. Doctor Hamman has mentioned the experiments of Doctor Craven, carried out in our laboratory several years ago, in which he was able at will to render the liver either resistant or susceptible to destruction by salvarsan according to the type of diet administered. It is, therefore, not impossible that dietary variation may be one factor responsible for precipitating hepatic necrosis in the human being following treatment with the arsenicals, just as it is thoroughly well known to be an important factor in preventing, or in intensifying, the destructive action of chloroform and of carbon tetrachloride upon the liver. This possibility should be carefully examined. Certainly, the question of the prevention of the hepatic damage produced by arsphenamine is worth the most serious clinical study, for treatment is very widespread, and as matters stand today a certain, if small, proportion of those who receive the drug are doomed to be killed by it.

CASE II.—S. T. Unit History No. 45193. Admitted September 4, 1932. Died September 6, 1932. A colored housewife, fifty-six years of age, entered the hospital complaining of "pain all over the body, and fever." She was somnolent and could not give a connected account of her illness, so the history was obtained from a daughter. The patient always had been well. She had had typhoid fever at sixteen years; an attack of grippe in 1925; and some vague illness, characterized by general aching, pain in the chest, sinking spells and shortness of breath in 1928. For twenty-five years she had had hay fever and asthma each fall, less severe during the preceding five years than before. Eleven days before admission to the hospital the patient had complained of being unusually tired. That evening she began to have general aching, most severe in the abdomen, sides, back and head. These symptoms continued and a few days later burning on urination and vomiting came on and slight jaundice was noticed. She also became drowsy and the speech was slurred. Four days before admission the drowsiness increased and off and on she was delirious. On the same day she had a shaking chill followed by high fever. The jaundice had become progressively more and more marked. For a time the patient seemed to improve a little, at least her mind cleared up, but the day before admission the lethargy again deepened and she had involuntary urination and defecation.

*Examination.*—Temperature, 102.6°; pulse, 110; respirations, 40; blood pressure, systolic 105 mm. Hg, diastolic 75 mm. Hg.

The patient was an obese colored woman, lying quietly in bed with closed eyes in a stuporous condition. She could be aroused with difficulty and then answered questions sensibly, though her attention soon wandered. Often she would stop in the middle of a sentence and not finish it. There was no speech defect. There was intense jaundice. The eyes were normally prominent, pupils reacted actively. The eyes moved normally. The fundi showed moderate arteriosclerosis but otherwise were negative. The remaining teeth were carious and there was gingivitis and pyorrhea. The tongue was dry and heavily coated. The pharynx showed no noteworthy abnormality. A few of the cervical glands were palpable, otherwise there was no glandular enlargement. The thyroid was not enlarged. The lungs were clear except for a few sonorous rales generally distributed. The heart was not enlarged; sounds were clear. The pulse was regular, equal at the two wrists. The peripheral vessels were not thickened. The abdomen was prominent and rounded. Normal respiratory movements were absent. The walls were tense but there was no true muscle spasm. The whole abdomen was tender, the tenderness more marked on the right side. Liver dullness extended two finger-breadths below the costal margin; the edge could not be felt. The spleen was not enlarged. The pelvic and rectal examinations were negative. There was moderate clubbing of the fingers. There was marked tenderness over the tibiae and along the spine. The neurological examination was negative.

*Course in the Hospital.*—Following admission the patient became somewhat more drowsy. From time to time she vomited. The abdomen always was tender and it became more and more distended. The surgeon called in consultation felt there was no indication for operation. Finally the abdominal distention became extreme, the tenderness more marked and vomiting more frequent. The patient died in this condition three days after entering the hospital.

*Laboratory Examinations—**Blood Count:*

9/4/32 Hbg. 92%. Red blood cells, 4,180,000. White blood cells, 21,500.

*Differential*

Myelocytes	1.0%
Juvenile neutrophils	16
Segmented neutrophils	77
Adult lymphocytes	5
Monocytes	0.5
Eosinophiles	0.5

Stained smear—No anisocytosis or poikilocytosis. No stippling, achromia or basophilia. No nucleated red blood corpuscles. Marked leukocytosis with shift to left. Platelets normal in number and size.

*Blood Count:*

9/6/32 Hbg. 78%. Red blood cells, 3,750,000. White blood cells, 21,400.

*Blood Culture:*

9/5/32 Diphtheroids.

*Blood Agglutination:*

9/5/32 No agglutination with *B. typhosus*.

No agglutination with *B. paratyphosus*—A.

No agglutination with *B. paratyphosus*—B.

van den Bergh Reaction—16 mg. direct.

*Cultures from Urine:*

9/5/32 Very slight growth *B. coli*.

9/6/32 Moderate growth *B. coli*.

*Urine Examination:*

Two specimens showed a small amount of albumin; no sugar; a large amount of bile and urobilin; a trace of acetone; no tyrosine or leucine.

*Microscopically:* Moderate number of white blood cells, a few hyaline and granular casts.

*Roentgen ray Examination:*

9/5/32 Abdomen: No gall stones can be demonstrated.

## DIAGNOSTIC DISCUSSION

The clinical manifestations of this patient's illness are somewhat confusing. As you scan the records a number of possible explanations for the sequence of events comes to mind but none of them seem to fit the facts easily and snugly. During the period the patient was on the ward there was a wide difference of opinion about the diagnosis and no agreement was reached. This uncertainty and confusion is reflected by the final clinical diagnosis which reads,



*Cholemia, cause undetermined; Septicemia? Acute yellow atrophy?* This conclusion, as you see, is sufficiently indefinite to satisfy each of the conflicting views. The situation, therefore, presents an interesting problem in diagnosis. We will begin by choosing a certain point of departure for argument and from this point proceed cautiously testing the ground step by step as we go along. For our purpose we will select one of the most pronounced and conspicuous of the symptoms, namely, jaundice, and from a consideration of the jaundice we may be led on gradually to discover the conditions which produced it and so in the end arrive at the underlying cause of the illness, thus establishing a satisfactory diagnosis.

The illness came on acutely with vague abdominal symptoms accompanied by the characteristic manifestations of infection, that is, fever, prostration, general malaise and later delirium. Jaundice did not appear until some days later but once having made its appearance it grew steadily deeper and deeper. The illness lasted from beginning to end but fourteen days and death came with the symptoms of profound intoxication. Under these circumstances we may suggest three possible explanations for the jaundice: 1) Necrosis of the liver cells, 2) Gall stones, 3) Suppuration of the liver.

In discussing the previous case we had something to say about necrosis of the liver so we need say but little now. However, this little will be sufficient for our purpose since no one familiar with the clinical symptoms of necrosis of the liver would accept it as a satisfactory explanation for the symptoms now being considered. Necrosis of liver cells results from the action of a poison, the identity of which we often but do not always know. The symptoms that follow may be acute and severe but they are seldom accompanied by the marked symptoms of infection. The evidence in this patient of deep intoxication may be interpreted to indicate hepatic insufficiency and this be urged as a point in favor of liver necrosis. However, the intoxication may have been the result of the infection alone and although it may have been due wholly or in part to hepatic insufficiency still some other form of liver damage may as well have been accountable for it. But as I have said the clear evidence of a severe infection is the strongest point against liver necrosis and furthermore in those rare instances in which a degree of liver necrosis sufficient to produce deep jaundice seems to be the result of some obscure infec-

tion, the jaundice comes late in the course of the illness and not early as it did in this patient.

The possibility of gall stones with concomitant inflammation of the bile passages was considered while the patient was under observation in the hospital, as is evident from the fact that a roentgenogram was taken to see if gall stones might be demonstrated. The roentgenogram was reported not to show gall stones. This evidence has only slight negative value since gall stones, even though present, may cast no shadow to the roentgen rays. However, the symptoms and their progress were not at all like the course of events characteristic of gall stones. The illness did not come on with the sharp pain of gall stone colic and the stormy symptoms of severe infection and deep intoxication are not those which usually accompany the impaction of a stone in the common duct.

In contrast to the difficulty of explaining the symptoms on the assumption that they were due to liver necrosis or gall stones, is the ease with which they fit in with the suggestion that they were due to suppuration in the liver. Wherever the disease may have started, it seems clear that early in its course infection of the liver must have occurred and that this was followed by extensive suppuration. This view satisfactorily explains the high fever, the marked leukocytosis, the profound intoxication and the deep jaundice.

If we agree that extensive suppuration of the liver is the most plausible explanation for the jaundice then we must go on to define more precisely the exact character of the suppuration. Again three possibilities come up for consideration, 1) A large solitary liver abscess, 2) A single abscess or multiple liver abscess in association with general sepsis, 3) Multiple liver abscesses due to infected emboli coming from an area of suppuration draining into the portal vein, suppurative pylephlebitis.

A solitary liver abscess of unknown etiology rarely occurs. The commonest form is the large amoebic abscess when there is no evidence of amoebic colitis. Solitary abscesses from whatever cause seldom run a rapidly fatal course and intense jaundice is unusual.

Occasionally a liver abscess occurs in association with general sepsis. Such an instance was presented at these conferences somewhat over a year ago and has been reported by Carter and Baker.<sup>9</sup> The infecting organism was the gonococcus. The patient had high

fever and a marked leukocytosis but no jaundice. When multiple liver abscesses occur in septicemia the symptoms of sepsis dominate the clinical picture and overshadow the manifestations of suppuration in the liver which are usually inconspicuous.

The symptoms exhibited by this patient are very characteristic of those which usually occur with suppurative pylephlebitis. Numerous infected thrombi reach the liver and these produce abscesses which extend and coalesce producing extensive suppuration. There is high fever, leukocytosis, profound intoxication and often deep jaundice. The illness runs a rapid course, the patient usually dying after from two to three weeks.

Having arrived at the conclusion that the patient had multiple abscess in the liver, we must now inquire after the source of the infection. There are three possibilities that must be considered, 1) Pelvic infection, 2) Infection in the urinary tract, 3) Infection in the gastro-intestinal tract.

Pelvic infections are so common, especially in colored women, that we must always consider this possible source of infection when there is evidence of infection elsewhere in the body. However, in this patient there was no evidence of pelvic infection since the pelvic examination was quite negative. Even though pelvic infection had existed it could not have been the cause of the liver suppuration unless it had extended and directly involved some of the structures draining into the portal circulation. The only other route by which infection in the pelvis could reach the liver would be through the general circulation and we have already pointed out that what happens to the liver under these circumstances is usually something quite different from what happened in the patient we are now discussing.

The presence of pus in the urine and the repeated cultivation of the colon bacillus from the urine demonstrate conclusively that there was infection in the urinary tract. That infection in this location could cause the symptoms we are considering seems most unlikely and for the very same reasons that make pelvic infection a most unlikely source. There is no direct connection between infection in the urinary tract and the portal circulation and we have already explained that infection carried through the general circulation produces a different clinical picture.

So we are forced to assume that the primary disease, to which all else was secondary, was an infection in the gastro-intestinal canal. Just where this infection was located we cannot definitely say but, since appendicitis is so far more common than any other acute infection in the abdomen, it is altogether likely that it was acute appendicitis.

By selecting one prominent symptom, jaundice, as the point of departure for argument we arrive gently and without logical violence at the conclusion that the patient had acute appendicitis. The conclusion seems to be reasonable but before we finally accept it we should, as it were, prove the result by now taking the conclusion and comparing it with the clinical picture to see if the two fit together accurately and smoothly. Assuming then that the patient had acute appendicitis we review the story of the illness and find that the assumption explains all the details easily and satisfactorily.

A healthy woman is suddenly taken ill fourteen days before death with acute appendicitis. The symptoms at onset are pain in the abdomen, fever and general malaise. Branches of the portal vein about the appendix become plugged with infected thrombi. Many of these thrombi become loosened and are carried to the liver where they produce multiple abscesses. As these abscesses extend jaundice comes on and at the same time the symptoms of infection become more pronounced and the evidence of intoxication appears which grows ever deeper and deeper. The tender abdomen becomes more and more distended, the patient begins to vomit and lethargy passes into coma.

Therefore, the diagnosis reads:

Acute appendicitis.

Suppurative pylephlebitis.

Multiple abscesses of liver.

#### THE LESIONS FOUND AT AUTOPSY AND THEIR RELATION TO THE SIGNS, SYMPTOMS AND CLINICAL DIAGNOSIS

At autopsy (No. 12760) the tissues of this patient were jaundiced, and the lesions which were found provided a straightforward explanation of the jaundice and of the other clinical signs and symp-

toms. These lesions are precisely those which Doctor Hamman has prepared you to expect.

The *appendix* is sharply bent upon itself in its mid portion, and at the angle of the bend the wall is necrotic and inflamed. Surrounding the appendix there was a localized area of infection about six centimetres in diameter composed of a series of small abscesses, in the center of which lay the appendix. The remainder of the peritoneal cavity was quite normal. These two *veins leading from the abscessed area* are filled with soft, infected thrombi.

Here, now, is the *liver* which, you see, is somewhat enlarged. Yellow clusters of small abscesses are visible beneath the capsule, and on section you see at once that the organ contains many small abscesses. The wall of the portal vein is thickened, its lining is roughened, and many branches of the vein in the substance of the liver are filled with purulent thrombi. Unfortunately, at the time of autopsy the connections between the portal vein and the periaependiceal veins were destroyed, so I cannot demonstrate to you the continuous path of infection leading from the region of the appendix to the liver. The bile ducts are patent. The gallbladder is normal.

In each *lung* there are several abscesses, the largest being two centimetres in diameter. The lung substance is everywhere else air-containing and normal.

There were no lesions in any other organs bearing significantly upon the patient's illness.

We shall now examine the affected tissues microscopically. This is the *wall of the appendix*, and you see that this section includes a portion which is necrotic. The wall is replaced by dead inflammatory cells which are continuous with the similarly dead cells of the inflammatory exudate about it.

Here is a section of one of the *neighboring veins*. Its wall is partly necrotic and its lumen contains a thrombus which at this point is undergoing organization, but here further along appears as a purulent mass containing clouds of Gram-negative bacilli.

In this section of the *liver* we come at once upon a large branch of the portal vein which is filled with an infected thrombus, and here are smaller branches plugged with polymorphonuclear leukocytes. As I move the section about you see vein after vein filled with purulent exudate. The infection has extended from many of these

smaller veins into the liver substance so that we encounter one small, fresh abscess after another in these various sections of the liver. Note that none of the *bile ducts* are inflamed. The process is purely a pylephlebitis and there is no cholangitis. The liver cells at a distance from the abscesses show in the periphery of the lobules a marked degree of cloudy swelling, associated with the generalized infection; those in the central parts of the lobules are in many places atrophic and shrunken. We shall discuss in a moment the significance of these alterations in the pathogenesis of the jaundice.

In this section of the *lung* you see that there is no appreciable emphysema in spite of the long history of asthma. Here we come upon one of the abscesses. It is relatively fresh, for there is no suggestion of beginning encapsulation.

Gram-negative, colon-like bacilli are present in abundance in the infected tissues about the appendix, in the infected periappendiceal and portal veins, and in the abscesses in the liver and lungs. The colon bacillus was cultivated at autopsy from the lesions in the liver and lung and from the heart's blood. The kidneys and bladder were normal. The colon bacilli cultivated from the urine must, therefore, have been excreted from the blood, just as typhoid bacilli pass into the urine from the blood.

The anatomical diagnosis is, therefore:

Gangrenous appendicitis.

Localized periappendiceal abscesses.

Suppurative thrombophlebitis of ileocolic veins.

Suppurative pylephlebitis.

Multiple abscesses of liver.

Septicemia (*B. coli*).

Jaundice.

Abscesses of lungs.

In this case, as in the last, the laboratory tests clearly indicated the presence of a regurgitation jaundice for there was a prompt van den Bergh reaction and bilirubinuria. The stools were well colored with urobilin, however, and this as we shall see is an indication that the jaundice was not a pure regurgitation jaundice. It must be pointed out that the mere loss of an amount of liver tissue represented by the numerous little abscesses would certainly not have

been sufficient alone to have produced jaundice, for a great deal of the liver substance remains uninvolved. Had the areas occupied by abscesses been merely tumor metastases replacing liver substance, for example, jaundice would not have appeared, for the remaining normal liver substance would have sufficed to free the blood from the normal amount of bilirubin produced and, in addition, from the bilirubin which might have leaked back into the blood from the canaliculi interrupted by the tumor nodules. But in this case two other factors were present which acted to precipitate the occurrence of jaundice. First, the hepatic substance unoccupied by abscesses was not normal. The cells were altered by the cloudy swelling attendant upon the generalized infection, and in many places they were atrophic as a result of the closure of branches of the portal vein by thrombi. Both cloudy swelling and atrophy serve to impair the excretory power of these cells. In the second place, one of the very common results of septicemia is increased red-cell destruction. The anemia resulting from this is often a factor, in itself, in the impairment of the excretory power of the liver,<sup>8</sup> but in any event the increased red cell destruction leads to increased bilirubin formation, and therefore, even in septicemias without extensive liver cell destruction, jaundice frequently occurs for the reason that a liver with an excretory capacity reduced by cloudy swelling and anemia is called upon to excrete increased amounts of bilirubin. The jaundice of that type, however, is characterized by a delayed van den Bergh reaction, highly colored stools, and the absence of bilirubinuria. The existence of a prompt van den Bergh reaction and bilirubinuria in the presence of septicemia in cases such as the present one points unmistakably to an hepatic involvement more severe than simple functional inability to excrete all the bilirubin formed. It indicates specifically the rupture of many bile canaliculi, permitting a reflux into the blood of the bilirubin which has been excreted into them.

In the present case, therefore, a liver with substance reduced by abscesses and otherwise impaired functionally, was called upon to take care of an increased production of indirect reacting bilirubin and, in addition, to free the blood from that amount of direct reacting bilirubin which leaked back into the circulation from the interrupted canaliculi. This it was not able to do successfully,

and jaundice made its appearance. It is obvious that in a case such as this one in which there are the elements of both a retention and a regurgitation jaundice as defined in the discussion of the preceding case, the overproduction of bilirubin may cause the stools to be well colored even though the tests in the blood and urine might lead one to expect acholic stools. This very fact is obviously important as a clinical indication that in addition to the anatomical lesion in the liver disrupting the bile capillaries there exists also a process (septicemia in the present case) causing an increased formation of bile pigment.

Appendicitis with periappendiceal abscess is the most common cause of pyelephlebitis, but while the former condition is common, pyelephlebitis is quite rare. There are only twelve cases of pyelephlebitis in the 12,000 consecutive autopsies performed in the Johns Hopkins Hospital between 1889 and 1933. This figure (.1 per cent.) agrees with that of Brown, who found pyelephlebitis in .12 per cent. of 9,494 autopsies performed at St. Bartholomew's Hospital.<sup>10</sup> Seven of our twelve cases had their origin in infection of the appendix. In one case the infection of the portal vein was traced directly to a localized abscess resulting from a strangulated hernia; in another to a diphtheritic gastritis; in two cases the portal vein was involved by the extension of infection from cholangitis, and in one case a large liver abscess encroached upon the vein. During this period there were 109 autopsies on patients dying of acute appendicitis. Thus only one out of nine of the *fatal* cases of appendicitis in our records was complicated by pyelephlebitis. This, of course, by no means represents the incidence of pyelephlebitis as a complication of acute appendicitis, for most cases of appendicitis are not fatal. It represents only the frequency with which pyelephlebitis was found in fatal cases.

It might be supposed that the development of knowledge about the origin of pyelephlebitis from infection of the appendix had to wait upon Fitz' memorable papers on appendicitis written in the 1880's. It is interesting to note, however, that such was not the case. Twenty-five years previously Frerichs, in his *Lehrbuch der Leberkrankheiten*, outlined in the clearest possible manner the clinical and pathological details of the condition, clearly delineating the manner of origin from gangrenous appendicitis, and the



propagation of the infection by way of the veins leading from the region of the appendix to the portal vein. Naturally, at that time he knew nothing of the bacterial nature of the infection. Among the cases of pyléphlebitis arising from appendicitis which he reviews there is one which, clinically and pathologically, is almost precisely like the case which we have had under discussion in this conference.

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# Recent Progress in Ophthalmology and Otolaryngology

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## I. A REVIEW OF THE LITERATURE CONCERNING DETACHMENT OF THE RETINA AND ITS TREATMENT\*

## II. THE RELATION OF THE PARANASAL SINUSES TO OCULAR DISORDERS

### A Review of the Recent Literature\*

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SINCE Professor J. Gonin devised his new operation for the treatment of detachment of the retina, this subject has become one of the vital issues in ophthalmology. There is no doubt that ophthalmologists stand in great debt to Gonin for having so successfully and energetically taken up this question. He paved the way for the introduction of later methods by Linder, Guist, Larsson and others, so that the prospects of effecting a cure for this condition, heretofore considered almost incurable, have become increasingly bright.

### DEFINITION

By detachment of the retina is meant, a separation of the two retinal layers, so that the pigment epithelium remains adherent to the choroid, and the inner percipient portion over a part or whole of the retina is separated therefrom. The intervening space between these layers is filled with fluid, the nature of which is either physiological or pathological.

Ormond describes "spontaneous" or "idiopathic" detachment of the retina as, "the condition of retinal detachment found without evidence of any concomitant gross pathological condition, and excludes growth, definite inflammation, gross traumatism, etc., the de-

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\* From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital.

tachment being unaccompanied by any of these factors and apparently having occurred spontaneously without any obvious visible cause. It is, however, generally allowed that some degree (not necessarily a high degree) of myopia may be present, or the condition may occur in old people where senile changes exist and without any traumatic history, or only a history of slight jarring, shaking, etc., of the eye or body."

#### ETIOLOGY

Stallard writes that two theories are generally held concerning the cause of simple detachment of the retina; the "mechanical theory" and the "diffusion theory." The mechanical theory maintains that simple detachment of the retina takes place under one or several of the following conditions:

- (a) When the intra-ocular pressure in front of the retina falls below the normal.
- (b) When the pressure behind the retina is increased.
- (c) When adhesions between the vitreous and the retina contract and pull on it.

Under normal conditions the retina is attached at the papilla and ora serrata, the remaining part lies in contact with the choroid, it is not attached to it. Elastic tissue is present in the sclera and choroid, but absent in the retina. In myopia the anteroposterior diameter of the globe increases, the intra-ocular pressure falls, and the retina being an inelastic structure may become detached at a point between the papilla and the ora serrata. The intra-ocular pressure falls when the output of aqueous humour is defective. This defect is due to an interference with the normal activity of the ciliary processes, either from inflammation of the uveal tract, or from contraction of the circular ciliary muscle and ciliary processes, in

Primary degeneration of the vitreous, perforating wounds of the globe, and perforating corneal ulcers, by lowering the intra-ocular tension, dispose to retinal detachment. A subretinal hemorrhage arising from a contusion of the globe, and exudates in patients suffering from chorioretinitis, may produce sufficient local pressure to cause a detachment.

The diffusion theory, according to Stallard, is based on the presumption that the retina acts like the animal membrane of a dialyzer. "The retina separates two physiological fluids. The fluid in the tissue spaces and lymphatics of the choroid possesses colloidal properties, whereas the vitreous is crystalloid in nature. The supporters of this theory believe that the smaller crystalloid molecules can pass through the retina by a process of diffusion."

The following is a summary by Stallard of the causes of simple detachment of the retina:—

- (1) Trauma. Concussion of the globe, subretinal hemorrhage, perforating injuries, perforating corneal ulcers, and occasionally operative procedures on myopes, cause retinal detachment.
- (2) Progressive myopia is accompanied by softening of the sclera, and compression of the globe by the extra-ocular muscles; the shape and length of the eye is altered, and the retina is subjected to abnormal stresses, culminating in detachment.
- (3) Inflammation. Iridochoroiditis, panophthalmitis, and retinitis by producing exudates and changes in the vitreous, may cause detachment of the retina. Hann and Knaggs have described two cases of bilateral retinal detachment occurring in patients suffering from albuminuric retinitis during pregnancy. Recovery was complete in both patients. Adamuk, Benedict, and Mussey have also recorded similar cases which recovered after the termination of labour.
- (4) Congenital detachment of the retina. Fernandez has seen bilateral detachment of the retina in two brothers; the detachments were present at birth and persisted afterwards. He suggests that congenital syphilis is a cause of this condition, but he was unable to make investigations in this particular case.
- (5) Parasitic, due to cysticercus.
- (6) Idiopathic. Czerny found that continuous concentration of the solar rays upon the retina of frogs, birds, and certain mammals caused a disintegration of the retinal pigment epithelium. The layer of rods and cones becomes separated

from the pigment epithelium. Streams of leukocytes appear among the debris of the broken retinal elements and thereby augment the subretinal fluid. Czerny submits this as a possible cause where no other can be found.

Professor Gonin first visualizes a change in the vitreous, and subsequently in the retina, which may be unobservable to ordinary ophthalmoscopic examination. A partial liquefaction of the vitreous takes place, and a localized or general thinning of the retina, also giving no definite ophthalmoscopic evidence. The retinal change, however, is often in the region of the ora serrata, and therefore not obvious to ordinary ophthalmoscopic view unless extraordinary means are taken, such as full dilatation of the pupils and pressure deliberately made outside by the finger, in the neighbourhood of the ciliary body.

The primary change in the vitreous is one of partial liquefaction. The evidence for this is the frequent presence of fine floating opacities in myopic and senile eyes, and the occasional presence of a deformation of the details of the papilla, which vary with movements of the ophthalmoscope, presenting a condition similar to that seen when viewing the fundus through an irregularly astigmatic lens or cornea; in addition, we can sometimes see a diffuse opacity in the vitreous associated with "floaters" or streaks, but it is allowed that the ophthalmoscopic evidence of a liquefied vitreous may pass unnoticed or give only very equivocal signs. With regard to the retina, Gonin suggests that the retina, like the choroid, may be subject to strain and stress, and may be the subject of thinnings, atrophic areas, holes, and tears. The retina as well as the choroid is more firmly attached at one place than at another. The optic nerve fibres secure the retina firmly at the optic disc, but the attachment at the ora serrata is thinner, more attenuated, and more likely to fail, either as the result of pathological conditions affecting the choroid, or a senile condition associated with the attenuation of the nerve fibres and its parenchyma. On the other hand, the choroid is more firmly attached to the ciliary body and yields in the region of the optic disc and macula.

The partial detachment and retraction of the vitreous turns that body into a heterogeneous system, consisting of (1) non-albuminous

watery fluid, and (2) the unaltered or only slightly altered vitreous gel. This condition has an importance, Gonin thinks, in causing an unequal strain on the thinned and degenerated retina, so that any sharp abrupt movements of the eye or body may result in a sudden pull on the friable membrane. Traversing the liquefied vitreous may be strands of vitreous jelly attached at one point more or less firmly to the *membrana limitans interna*, and any abrupt sharp movement may cause a definite localized strain or pull at a point in the retina. The presence of any fine adhesion, the result of a small localized inflammation, would fasten the retina at such a point to the underlying choroid and would form an attachment which, as a result of even very slight trauma, would allow a tear to take place if the surrounding area were only supported by a liquid vitreous.

Gonin believes that detachment of the retina only takes place if a tear or hole exists in the retina, and that this hole allows the liquid vitreous to pass through it and so raise the retina from its bed on the pigment epithelium. These retinal tears are usually situated, in recent cases, on the convexity of the detachment, but if and when the fluid shifts further round or down, then the tear may be found at a spot where the detachment has become less raised. Another area where the tears are often found is in the region of the *ora serrata*, because it is here that the retina is thinnest, most vulnerable, and liable to degenerative and pathological changes either from cystic degeneration or *chorioretinal atrophy*. Holes in the area behind the equator are less common, and more often than not are the result of gross traumatism or definite pathological change.

Gonin observes that in macroscopical specimens of spontaneous retinal detachment there is no gelatinous clot behind the retina—that is to say, no coagulable exudate the result of inflammation. The preretinal and subretinal spaces are filled with an identical fluid of a watery nature. The vitreous gel is retracted forward, and is best and most abundantly seen between the equator and the *ora serrata*, and shows more or less extensive adhesions with the retina. These macroscopical specimens frequently disclose the presence of a hole or tear.

A simple progressive stretching, Gonin states, is not sufficient to detach the retina from the choroid, as was originally supposed to be the case in myopic detachment; on the contrary, the retina can

adapt itself better than the choroid to a gradual enlargement of the globe; the retina yields only to a sudden tension, and is torn either at the ora serrata or at some point where vitreous bands are adherent to the retina, a condition which is pathological; normally, the retina is not displaced even in complete liquefaction of the vitreous, unless some pathological cause has produced adhesions between the vitreous gel and the retina, and if a contusion occurs it results in a sudden abrupt pull on the thinned degenerated friable retina.

#### TREATMENT

Before Gonin devised his operation for detached retina, the therapeutic measures used in the treatment of this condition were regarded with almost universal scepticism, so that detachment of the retina, both to the laity and the medical profession, maintained the unenviable reputation of being almost incurable. Complete re-position of the detached portion of the retina, and restoration of function in this part is the aim and object of treatment. Re-position of the retina to the pigment epithelium is recognized by the return of a uniform red reflex, the disappearance of the characteristic fundus changes, and the restoration of the visual acuity and the visual field to normal. It may be partial or complete.

The collection of subretinal fluid separating the detached retina from the pigment epithelium is one of the principal factors preventing the coaptation of these two layers. The choroid exercises very feeble absorptive powers compared with other vascular membranes, so that the subretinal fluid is absorbed very slowly, and in some cases not at all. Meanwhile the detached part of the retina undergoes degenerative changes, and becomes converted into a fibrous structure covered with albuminous droplets, and incapable of functional restoration. Meyer Weiner believes that the retinal blood vessels exert a contractile force and thereby prevent reposition of the detached part. Retino-hyaloid adhesions may also prevent the detached part from resuming its normal position.

The fundamental principle of treatment is to cause coaptation of the detached retina and the choroid by establishing drainage of the subretinal fluid, and if necessary, by dividing any fibrous tissue bands between the vitreous and the retina.

There are two methods generally adopted for the purpose of draining the subretinal fluid:—

- (1) To increase the absorptive and excretory powers of the body by the administration of diaphoretics and diuretics, e.g., hot air baths, purgatives, injections of pilocarpine, salicylates, and the local injection of hypertonic saline solutions into Tenon's capsule.
- (2) Operative procedures such as scleral puncture, scleral trephine, and scleral puncture with permanent drainage by the introduction of horse-hair or gold wire.

To induce cohesion between the retina and the choroid, attempts have been made to set up inflammation by applying a cautery to the sclera over the site of the detachment, or puncturing the detached portion of the retina in several places, or by electrolysis, and by the injection of iodine in glycerine into the subretinal space.

Stallard divides the treatment of simple detachment of the retina into the following headings:—

- (1) Prophylactic.
- (2) Conservative.
- (3) Operative.

(1) Prophylactic treatment is directed toward the prevention of progressive myopia, and the onset of iridocyclitis. In progressive myopia, the globe lengthens and the vitreous liquefies and shrinks. In such cases the refractive error should be corrected fully and the patient's general health supported. Young persons must wear the full correction constantly, and elderly persons the full correction for distance, with an adequate deduction for near work. In order to avoid excessive convergence, near work must not be brought closer than 33 cm. Overaction of the internal recti during convergence compresses the sclera and thereby lengthens the globe. Particular attention must be paid to the following points in ophthalmic hygiene:—

- (a) The source of illumination must be placed behind and to the left of the patient, and must be of adequate intensity.
- (b) Reading and writing must be reduced to the minimum amount possible.



- (c) Close work must be engaged in for short periods only.
- (d) Recreation of a gentle nature is recommended, but games which are likely to cause jolts, blows, or excessive muscular strain are forbidden.

(2) Conservative treatment. Some general indications for guidance are necessary before deciding on the course of treatment suitable for each particular case. The etiology and the condition of the vitreous, retina, and choroid play an important role in this decision. The essentials of conservative treatment are:—

- (a) Absolute rest in bed. The position in which the head is placed varies with the site of detachment; i.e., if the detachment is in the region of the posterior pole the head must be immobilized in the horizontal position; if at the periphery and in the lower half of the retina, the head must be raised to the requisite angle. The patient must be fed, washed and nursed without moving his head. The bowels must be carefully regulated, and any physical exertion avoided. Any tendency to cough or sneeze must be checked, if necessary, by sedatives.
- (b) Therapeutics. To promote absorption of the subretinal fluid and to stimulate the excretory organs, hot air baths, saline purges, injections of pilocarpine hydrochlorate, iodides, and salicylates are administered in suitable doses.

(3) Operative treatment. The surgical history of simple detachment of the retina up to 1929 is reviewed by Stallard.

1860-70. Ware and Sichel were the first to suggest scleral puncture and the evacuation of the subretinal fluid. A little later Sir William Bowman, von Graefe, Alt, and Secondi performed the operation of discission of the detached portion of the retina, to allow the subretinal fluid to flow into the vitreous. This operation was soon abandoned owing to lack of success. de Wecker and Masselon then introduced the operation of scleral puncture at the site of detachment, and passed a gold wire drain into the subretinal space. This operation was a failure and was quickly abandoned.

1872. Shortly after this Wolfe and Snell performed meridional sclerotomy, puncturing the sclera in two places, and the detached part of the retina in several places.

1890-95. de Weeker and Chevallereau applied a canterly to the sclera at the site of the detachment. About this time Schoeler recommended the injection of a solution of iodine in glycerine into the subretinal space. The results of this practice were disastrous and it has been abandoned.

1891. Deutschmann divided cicatricial bands in the vitreous and at the same time injected the vitreous of rabbits in order to increase the bulk of the patient's vitreous. A little later Birch-Hirschfeld modified this operation by aspirating fluid into the vitreous. A severe inflammatory reaction followed these procedures, and owing to the rapid absorption of the injected fluids, the vitreous returned to its previous bulk in the course of a few hours.

1897. Muller's operation of choroidodialysis has been tried by several continental surgeons. The scleral laminae are divided layer by layer down to the choroid and a spatula is introduced between the sclera and the choroid, and made to pass in an oblique direction, finally it punctures the choroid at the site of retinal detachment, and is then withdrawn. Muller has also practised resection of the sclera to diminish the size of the globe, and to lower the tension of the choroid in cases of myopia.

1896. Electrolysis was tried by Montgomery, Snell, Terson, Motais, and others. The sclera was punctured by a platino-iridium needle and this needle was pushed through the sclera and on into the subretinal space. A current of five milliamperes was passed for one minute. The operation is very painful and the postoperative reaction intense. The results were not satisfactory.

Of recent years, attention has been turned toward the treatment of detachment of the retina by the injection of hypertonic saline under the conjunctiva or into Tenon's capsule over the site of the detachment. The object of this procedure is to drain subretinal fluids by osmosis; the choroid and sclera are assumed to act as a dialyzing membrane. Stallard thinks this hypothesis is fallacious. First, the subretinal fluid possesses a high albumin content, and is therefore of a colloidal nature, whereas the injected saline is a crystalloid solution. This being the case, the larger colloid molecules will not pass by osmosis through the choroid and sclera to reach Tenon's capsule. Secondly, the thickness and the dense fibro-elastic structure

of the sclera will afford mechanical difficulties to the passage of molecules between the two fluids.

September, 1923. Bettremieux described the operation of non-perforating pericorneal sclerectomy. The object of this operation is to improve the intraocular nutrition by making an anastomosis between the subconjunctival pericorneal vessels and the intrascleral plexus of veins.

The statistics for most of these methods are unreliable because of the limited number of cases collected. Of the 100 cases reported by various authors, only thirty-eight were followed for a period varying from one to three years after discharge from the hospital. The high percentage of recoveries in cases treated by conservative means can probably be explained by the favourable prognosis in all patients where the detachment is associated with albuminuric retinitis of pregnancy and eclampsia. These cases usually recover without any treatment. In myopes the prognosis was found to be worse than in hyperopes or emmetropes. In eyes affected with disease or previous injury, the prognosis is bad.

Some idea of the unfavourable attitude, toward the prognosis of detached retina, held by many ophthalmologists, can probably be obtained by the well known statistics of Doctor Vail (of Cincinnati): among 281 replies from oculists of the United States whom he had asked for information, he found that 250 of them had never cured a single case, while only thirty-one met with cures (twenty-five with a single cure each), so that the permanent successes were hardly one in every 1000 cases.

At the International Congress of Ophthalmology held in Amsterdam, in 1929, Professor J. Gonin described his method of treating simple detachment of the retina, based on the following conclusions gathered from a large amount of anatomical and clinical material.

He states (a), in most, if not in all cases of so-called "spontaneous" or "idiopathic" detachment, one or several tears may be seen in the retina. (b) The production of the tears is due to the vitreous humour dragging on the retina at the site of previous adhesions between both tissues, those adhesions having been formed in the neighbourhood of disseminated foci of chorioretinitis, which are frequent in myopic and senile eyes. (c) The presence of a hole, allowing the fluid of the vitreous to pass behind the retina and maintain-

ing thus the subretinal collection of liquid, explains the ophthalmoscopic appearance of the "spontaneous" detachment much better than the hypothesis of an exudation from the choroid. In the forms caused by such an exudation (detachments of pregnancy, in Coats' disease, associated with tumours or acute inflammations, etc.), the clinical course is also quite different.

According to Gonin, "the retinal tear being thus the determining cause of the 'spontaneous' detachment, and preventing it from healing, it was obvious that all therapeutic methods hitherto in use were unable to secure any permanent cure, the danger of a recurrence lasting as long as the hole in the retina remained open. Particularly, the many treatments the purpose of which is to give exit to the subretinal fluid or to promote its resorption, such as scleral punctures or draining, diaphoresis, subconjunctival injections, etc., were condemned as useless, inasmuch as they did not hinder the continual passing of liquid through the rent in the retina. This explains the habitual failures of those treatments and the general scepticism which is met with among most ophthalmologists, many of them thinking that even an attempt at cure is not worth making."

Ormond, having had the good fortune to see Professor Gonin operate and to have his views explained to him personally, describes the Gonin technique in detail, as follows:

The operation is not difficult and carries no greater risk than is incurred by the time-honoured cauterization of the globe, which is done for the purpose of establishing drainage for the subretinal fluid and a possible anchoring of the retina to the choroid by the production of a contracting scar. But Gonin's whole point is that it is useless to attempt this cauterization anywhere save in the immediate proximity of the tear. The cauterization must involve the tear, the whole tear, and as far as possible only the tear, to effectively close the hole and "nail" the retina to the choroid by means of a contracting cicatrix. Much time and care must be exercised to locate the spot where the cautery is to enter. The operation is not applicable if the hole is in the region of the optic disc or macula. If the hole is large or multiple, then more than one cauterization will probably be necessary, and if it cannot be reached by reason of its position in the eye then the case is not one for his operation. About 22 mm. from the

corneoscleral margin seems to be the practical limit of attempt, and even such a point would be difficult to reach with precision.

Search long and diligent must be made to locate the hole, and until it is found it is useless to attempt the operation. When it has been found, it should be accurately localized and the meridian in which it lies marked by a definite technique, so that no hesitation occurs at the operation. The globe is divided for localizing purposes into various planes indicated according to a clock face: vertical, XII-VI; horizontal, III-IX; down and out, and down and in, II-VIII; IV-X, etc.

The meridian, being decided on, is indicated by two small points made at the corneoscleral margin just under the conjunctiva by means of a pin dipped in India ink. Having fixed the meridian, the next point in the localization is to decide how far back the hole is from the ora serrata or from the most extreme point visible to the ophthalmoscope with fully dilated pupil and the eyeball rolled out to the extreme periphery. Professor Gonin has laid down certain figures for our assistance here.

The diameter of the optic disc represents 1.5 mm., the distance from the ora serrata to the limbus is taken as 8 mm., so that if the tear appears to be 4 discs' breadth from the extreme periphery of the visible fundus, with the pupil widely dilated, the tear would be  $8 + 6$  mm. from the corneoscleral margin = 14 mm.

Having found the tear, aligned the meridian, and measured the distance from the corneoscleral margin along that line, and having marked externally on the limbus of the cornea two spots representing the meridian, the surgeon is in a position to decide if he can reach the spot indicated with his cautery. The operation is done under a local anesthetic and the ordinary surgical technique is carried out.

Before operating, Professor Gonin marks his meridian by passing a fine silk thread through the conjunctiva, immediately over the further spot of the two, thus marking the meridional alignment. This thread is knotted and drawn through just as a seamstress does when starting to sew, and is used to indicate the meridian, because with the manipulation of the tissues, blood and fluid appear inevitably when the operation starts, and the mark previously quite obvious may become obscured; whereas the thread can always be found and made to connect the two spots indicating the meridian, so that the

surgeon is never at a loss to recover his alignment during the operation should his marks become obscured. The thread is inserted on the inked spot furthest from the tear, and should eventually connect three points—namely, the two marked with India ink and the exact point at which the cautery is to enter the globe.

The sclera is laid bare over the area which has been found to correspond with the tear seen within the eye, and by means of calipers the distance from the corneoscleral margin along the meridional line is measured to a fraction of a millimetre. This spot is marked by the pointed arm of the calipers being dipped in an alcohol solution of gentian violet, so as to mark definitely the exact spot which the surgeon, after prolonged care and calculation, has concluded represents the external point immediately over the hole in the retina. A Graefe's knife is now entered through this spot, the cutting edge of the knife being directed towards the cornea, and the depth to which it is inserted being dependent on the condition of the detachment; if subretinal fluid begins to flow out, the knife must have reached the space just external to the retina and the loss of some of the fluid may allow the retina to fall back nearer the sclera. The knife is withdrawn now, and if the operator inserts his glowing cautery he will produce a "sphere of influence" that is likely to involve the retina at the position of the tear. That this happens in some cases, probably in many, is now, I think, definitely established. The heat is sufficient to burn the margin of the sclera, the choroid, and to radiate through the intra-ocular fluid and inflame the retina. This cauterization produces an area of inflammation which, in a few days' time—nine to twelve—causes a contracting scar which ultimately settles down after the inflammation has ceased. In this way it is certainly possible sometimes to close the hole, "nail" the retina to the choroid and sclera, and, if Professor Gonin's conclusions are correct, cure the detachment, the subretinal fluid being absorbed, provided that the communication with the vitreous chamber through the hole is completely closed.

Gonin sums up his experience with 250 patients and about 300 operations as follows:—

(1) In more than 95 per cent. of the cases, whenever ophthalmoscopic examination is possible, one or several holes may be detected in the retina if looked for with sufficient care.

(2) In about 10 per cent. of these cases the hole is not in the retinal tissue, but consists of a rupture or tearing away from its insertion at the ora serrata ("disinsertion of the retina").

(3) In all recent cases, when the hole or tear has been closed up, cure is immediate, complete and permanent.

(4) In older cases (several weeks or months), closing the tear stops the detachment and may produce a more or less complete reposition of the retina, but restoration of the vision remains generally incomplete.

(5) If the detachment relapses, it is found that the tear has not been completely closed or that another tear had not been previously seen.

(6) A recurrence of detachment in a different region of the eye is due to formation of a new hole in the retina.

(7) Definite cure may be obtained in about 60 per cent. of recent cases, this percentage diminishing with the age of detachment.

Gonin states: "Not only is this proportion of cures a sure improvement in comparison with the former rarity, but the length of the treatment is far short of the many weeks or months of absolute rest in bed with both eyes bandaged, which was up to this time the most usual torment for the patients."

For a more accurate localization of the hole in the retina, Linder uses a binocular giant ophthalmoscopic with a special perimetric arm attachment. He has compiled a special chart for accurate and quick calculation from the measurements obtained.

J. Lijo Pavia uses the Nordensen retinal camera for cases in which the hole is seen to lie posterior to the equator of the eyeball. Many pictures are taken and superimposed on one another to establish a complete view of the retina as far as the equator. From this the meridian in which the hole lies and its distance from the limbus are easily calculated.

Larsson believes it has not been proved beyond doubt that rupture (hole) is the immediate cause of detachment of the retina, for cases have been observed in which such holes cannot be detected in spite of the closest search. He contends further, however, that the rupture, whether primary or secondary in nature, constitutes a formidable bar to reattachment and that closure is of the utmost importance for a favourable operative result.

Gonin asserts that if the hole is closed by operation, reattachment

of the retina takes place. Larsson believes that this thesis can equally well be reversed: "When reattachment of the retina takes place and the retina becomes adherent to the choroid, the hole heals or becomes obliterated. When Gonin fails in his operation, he blames the non-closure of the hole, which remains in its original state. This thesis can also be reversed: The hole remains because the retinal detachment still persists and the retina is not in contact with the choroid."

Larsson's aim has been to establish a wide adherence of the detached retina to the underlying tissue, this area to include the portion of the retina within which the hole is located, or, when no hole is present, where the detachment comes first in evidence. This goal he has tried to reach by making use of electro-endothelmy transclerally, obtaining a deep thermal effect without necrotization of the sclera. The method of operation he describes thus:

The conjunctiva is detached at the corneoscleral boundary and stripped off over an area corresponding to the extent of the retinal detachment. The globe is carefully exposed. In order to gain complete access to the globe a canthotomy is, as a rule, carried out and, if necessary, the tendinous attachments of one or more muscles are divided. The conjunctiva is kept away from the operative field by sutures held and fixed by artery clamps, so placed that the conjunctiva is thereby held expanded and the sclera kept free. After careful arrest of bleeding, best done by electro-endothelmy (with a needle-shaped active electrode), the endothermal treatment proper is begun.

The large indifferent electrode made up of a lead plate is applied to the leg or thigh; to obtain good contact the lead plate is not fixed directly on the skin, but an intervening gauze pad soaked in common salt solution is applied. The lead plate is bound to the leg by means of a gauze bandage, so as to obtain complete contact over a large surface area. This is important to prevent burns. As the active electrode, a metallic ball, 0.66 mm. in diameter and provided with a handle, is used.

An extremely weak current is used; on contact between the active electrode and the terminal of the indifferent electrode, the amperemeter of the apparatus generally gives a reading of from 1 to  $1\frac{1}{2}$  amperes. On contact between the active electrode and the sclera the current is too weak to give any reading on the amperemeter (less than 100 ma.). At several places, a few millimetres apart, the



active electrode is brought in full contact with the exposed sclera for five seconds at the most. To avoid contact with the ciliary body, the treatment is carried out at a respectful distance from the limbus, from 8 to 9 mm. This is done in order not to risk the production of cataract or other complications that may conceivably arise from damage to the ciliary body. The thermal effect on the sclera is evident as an opaque, generally dark-colored, annular zone corresponding to the place of contact. The sclera is also seen to be flattened out in a peculiar manner near the treated area. The heating being completed in the manner described, trephining of the sclera is carried out within the treated area with an Elliot trephine. This is preferably done at a place corresponding to the most dependent area of the detachment. On carefully dividing the exposed choroid the subretinal contents escape, whether these are made up of a more or less thin fluid or more normal vitreous humour. No bleeding occurs at the trephine wound, probably owing to coagulation of the blood as a result of the preliminary endothermal treatment. The escaping fluid or vitreous humour is washed away with physiologic solution of sodium chloride. Trephining is carried out partly with the view of removing subretinal fluid, and partly to prevent a subsequent increase of intra-ocular tension or reaccumulation of subretinal fluid. When the operation has been completed in the manner described, the resected muscles and conjunctiva are sutured.

The patient is kept in bed with both eyes bandaged for a fortnight. The head is placed as far as possible in such a position that the detached area lies inferiorly, with the view of furthering important mechanical factors that may help to approximate the retina to the eyeball. In the case of a favourable result the patient is then kept in bed for another eight to fourteen days, but without bandage. Atropine is given as long as the eye is inflamed.

At first the operation was carried out over a very large area of the sclera, corresponding approximately to the extent of the retinal detachment. Nowadays in cases of complete or extensive detachment, I confine the operation to that quadrant or portion of the globe within which the hole is located. *No precise localization of the site of the hole is necessary.* In cases in which no hole can be demonstrated, and in cases of large detachments, the electro-endothermal treatment is carried out over a larger area, but particularly within

that part where the detachment first came into evidence. To this end the history may be of great value.

The endothermy apparatus that Larsson uses is Siemen's "Thermoflux K."

Larsson performed this operation on forty out of fifty-five patients with detachment of the retina, who applied for treatment. He stresses the importance of distinguishing operatively favourable cases from unfavourable ones. He believes that those cases seem to offer the best prospect in which the detachment has not been present for more than a few weeks. The chance of operative success seems to be less favourable for elderly people (over fifty or sixty years).

In Larsson's series of forty cases, twenty of them got a complete reattachment of the retina. In other words, his percentage of successful cases is fifty.

In comparison to Gonin's operation, Larsson believes that his method possesses the following advantages:

- (1) By creating a more widespread adherence between the retina and the choroid, fresh detachment, like fresh holes, arises less readily in the area adjacent to the primary lesion. On this account, occurrences arise perhaps less readily and the operation need not be repeated so often.

- (2) Bleeding rarely occurs, owing to the thermal effect on the vessels, such as coagulation and thrombosis.

- (3) As the thermal effect takes place from without and not by the introduction of a cautery point into the vitreous humour, no cicatricial plug is obtained in and toward the vitreous from which traction can take place in the retina leading to fresh detachment and holes.

- (4) The operation is easy to perform and there is no necessity for the precise localization of the hole in the retina.

Guist, working in Vienna, has based his operative procedure on the cystoid degeneration theory of the cause of retinal detachment. Knowing that cystic degeneration usually affects the peripheral portion of the retina and the fovea, he believes that retinal tears usually occur in two elective places in the retina. One, the ora serrata, or at a distance of 8-10 mm. behind the ora serrata; the other, at the fovea. These areas are weakened and when an injury or stretching of myopia occurs, the cyst becomes transformed into a hole, the retina balloons out, and the vitreous passes through.

Guist was struck by the lessening success of the Gonin operation during the past few years, and he found that the retinal damage in the neighbourhood of the cautery frequently led to relapses that were, at times, accompanied by the formation of holes larger than the original ones. He found that cauterization of the new holes were mostly without success, and on repeated ignipuncture, Guist and his co-workers found bleedings into the vitreous body. Upon examination of an enucleated eye, which had been lost through an intra-ocular inflammation, it was noted that the hole or rupture of the retina had become glued to the choroid along its edges, and the vitreous body between the cleft and the choroid was loaded with polynuclear leucocytes and some fibrin, and, that some new vessels were formed in the neighbourhood of the adherent spot. This inflammatory reaction, causing adhesion of the retina to the choroid, brought Guist to the point where he thought that a chemical action, causing a fibrinous exudative reaction, would bring about the desired results. KOH causes this type of reaction, and it dissolves collagenous connective tissue, which is the cause of the ensuing inflammation. He experimented on animals for determination of the time required to cause an exudate, always keeping in mind that he did not want to injure the retina. Adelman describes the technique devised by Guist:—

The hole, or holes, are first thoroughly localized. Guist uses a giant Gullstrand ophthalmoscope, but many men have used other methods with equal success. Meek, of New York, has worked out a very simple method of localization with a ring that attaches to the limbus. A plan, or drawing, of the fundus is made. The eye is then cocainized, and complete akinesis is done. The conjunctiva is dissected back, and, if the tear lies under a muscle, that muscle is resected and drawn out of the way. The sclera is cleaned and a dry field obtained. If there is any bleeding, gauze is applied until the bleeding ceases. Care should be taken not to work over the course of a vortex vein or a ciliary nerve. Exact localization of the tear should be marked out on the sclera with superficial thermocautery, or with India ink. Then a trephine, 1.5 or 1.75 mm., very sharp, is gently rotated, and the tissue teased out until the choroid is exposed, being careful not to cause hemorrhage nor to perforate the choroid. After all trephines have been made, a small stick of paraffin-covered KOH is applied; the wax tip should not be cut off until just the

moment before the KOH is to be applied, because KOH is very hygroscopic. The field is then thoroughly dried, and KOH applied for half a second, and immediately neutralized by applicators soaked in 0.5 per cent. acetic acid, and the field is then thoroughly washed with salt solution.

Touch, neutralize, and wash, is the procedure for each hole; then dry. A blunt probe is then gently pushed through a few trephine holes and through the choroid to permit escape of subretinal fluid. The muscle is then sutured, conjunctiva sewed, both eyes bandaged, and patient sent to bed.

After several days the bandage is removed, and a pair of blank frames, with small holes in the middle of the blank, are worn so the patient looks directly through the holes. The sides of the frames are covered with celluloid. After absolute quiet and rest for several weeks, the patient is discharged, but many follow-up examinations have to be made.

Of course, a true valuation of this type of operation cannot be formed until a long series of cases have been studied. Guist has claimed, in a personal talk with Adelman, that his cures range from 65 per cent. to 91 per cent., stating that if he chooses his patients as Gonin does, he gets 91 per cent. of cures, but that if he operates upon every patient, regardless of duration and type of detachment, he gets only 65 per cent. of cures.

Linder is not quite so sanguine about the percentages. However, the true valuation cannot be determined for some time to come. The operation does not remove the cause of detachment, but as in glaucoma, the cause has not yet been definitely determined.

In conclusion, it can be said, based on the statistics available, that the operative methods for the treatment of detached retina, in use since 1929, have increased the number of cures from less than 5 per cent. to approximately 50 per cent. There is no doubt that Gonin has made a great contribution to ophthalmology, by stressing the importance of the rent or hole in detached retina, and the necessity, for successful treatment in these cases, of closing this communication between the vitreous chamber and the subretinal space. The chief objections to the Gonin operation seem to be the difficulty in an accurate localization of this hole and the likelihood of producing more rents in the retina, necessitating a repetition of the operation. The endotherapy method is the easiest to perform but requires

elaborate electro-surgical equipment. The Guist method requires usually one and a half to two hours of careful scleral trephining and painstaking dissection to avoid excessive injury to the choroid with resulting hemorrhage. This method, however, is meeting with more favour in most of the American Clinics. At the Wilmer Institute, almost every case treated in this manner, during the last year, has been successful. Time and more statistics of cases observed by follow up examinations, over a longer period than those already reported, alone, will serve to evaluate the true worth of surgery in detached retina.

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## II. THE RELATION OF THE PARANASAL SINUSES TO OCULAR DISORDERS

### A Review of the Recent Literature\*

THERE are, as was stated by Gifford, certain phases of the relationship between the eye and the paranasal sinuses which are apparently so well understood as to require little or no mention. In the case of frank orbital cellulitis, the sinuses are always suspected if nasal examination and roentgenograms present evidence of infection. Gifford believes that where the sinuses are incriminated in such cases, the infection is usually a purulent ethmoiditis or sphenoiditis, which leaves no doubt of its etiologic importance, and that in the other cases some cause for a metastatic infection can be located elsewhere in the body.

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\* From the Wilmer Ophthalmological Institute of the Johns Hopkins University and Hospital.

The sinusses, as foci of infection causing uveitis, episcleritis and deep keratitis, are always kept sufficiently in mind by most ophthalmologists, although the association, Gifford believes, is not nearly so frequent as one would suspect from the frequency of sinusitis in our climate. McKenty believes that chronic sinusitis in northern climates is so common that the finding of microscopic evidence of the disease has little or no significance. He believes that thousands of people have diseased sinusses and are entirely unaware of it. Unless something arises to break down the immunity of these patients to their local infection, health equilibrium is maintained; but once their resistance is disturbed trouble begins. The eye is but one target in many for the flood of infection which thus may enter the system. Gilbert and Bulson (quoted by Gifford) found 4 per cent. of their cases of uveitis due to sinus disease. Brown and Irons found only 2 per cent. while Newton found 8 per cent. of such cases in their series of iritis. In 188 private cases with uveitis, Gifford found that 0.8 per cent. seemed to be due to sinusitis. In McKenty's series of fifty-eight cases with uveitis about 60 per cent. were greatly improved following radical operative treatment on the sinusses.

The phase of the subject which has been of most interest to ophthalmologists, otolaryngologists and neurologists alike, is the relative importance of the paranasal sinusses in the causation of retrobulbar neuritis.

In neuritis intra-ocularis the disc is altered in color, being either whitish gray or reddish, is enlarged laterally so as to appear bigger than normal and is more or less prominent. The retinal arteries are thinner while the veins are distended. Retinal hemorrhages are often present near the disc and not infrequently also in the peripheral fundus. In retrobulbar neuritis the inflammation is confined to the orbital division of the optic nerve, and, in the restricted sense here used, is confined to the axial portion of the nerve trunk. At first, ophthalmoscopic examination shows either no changes at all in the papilla or changes that are insignificant; but later, changes in the papillomacular bundle may cause a wedge shaped area of pallor on the temporal side of the disc. Wilmer has noted, several times, in very severe cases with much reduced vision, small hemorrhages in the retina approximately between the papilla and macula. Actual swelling of the disc has been noted by some observers (quoted by Wilmer). Retrobulbar neuritis must be distinguished from a

descending neuritis, which likewise affects the retrobulbar segment of the nerve but ultimately also extends to the disc.

Some of the causes of optic neuritis, as given by various authors, are: 1) brain diseases; 2) syphilis; 3) tuberculosis; 4) the acute infectious febrile diseases, including erysipelas, mumps, influenza, tonsillitis, measles, pneumonia and malaria; 5) toxic conditions caused by disease of the kidneys, extensive skin burns, methyl alcohol, the excessive or long continued use of quinine, salicylates, arsenic, iodoform, tobacco, ethylhydrocupreine and rarely carbon monoxide; 6) multiple sclerosis; 7) infection of the accessory nasal sinuses.

Gifford has resolved the question of the relationship between sinus infection and retrobulbar neuritis into three parts. In what percentage of cases of retrobulbar neuritis is sinusitis the cause? Can retrobulbar neuritis be caused by disease of the sinuses giving no evidence on rhinological or roentgenological examination and if so what is the pathology of such sinus disease? In the presence of retrobulbar neuritis with no apparent cause and with no nasal evidence of sinusitis shall we advise exploratory operation on the sinuses?

The first question has received widely varying answers. Meller (quoted by Gifford), found 4.5 per cent. which he considered rhinogenic among the Vienna cases for two years. Lang found 3.5 per cent., Heine 3 to 6 per cent. and Langenbeck 3.5 per cent. of such cases. Scheerer and Maier found definite multiple sclerosis as the cause in 5.5 per cent., tobacco and alcohol abuse in 5.5 per cent. and sinusitis in only 1.5 per cent. In 11 per cent. no cause could be found. Weill, out of thirty-five cases, found only one with ethmoiditis. He believes that few cases are improved following sinus operations. Redslob with material from the same city is convinced of the importance of sinusitis in retrobulbar neuritis (quoted by Gifford).

Wilmer states that an estimation of the relation of diseases of the paranasal sinuses to axial neuritis varies all the way from being considered negligible to being held as the chief factor. In his series of thirty cases out of 5,058 admissions to the Institute for survey, eighteen were followed for some time. In 11 per cent. of these the probable cause was sinus disease.

Woods and Rowland, in a series of 138 cases of various optic neuropathies, in which the diagnostic study had been either com-

plete or sufficiently complete to leave no doubt as to the actual etiological factor responsible, found that 8.5 per cent. were believed to be due to posterior sinus disease for three main reasons:— (1) In none of them was there any evidence of multiple sclerosis; (2) the acute cases cleared up promptly after radical drainage of the posterior ethmoidal and sphenoidal sinuses; (3) in the chronic cases with optic atrophy, although operation was without effect in improving the vision, the medical survey was negative except for a manifest infection in the posterior ethmoids and sphenoids. In two cases of the series, in which a diagnosis of multiple sclerosis was justified and in which there was some evidence of posterior sinus disease, operation on the sinuses was without effect on the eye picture.

Le Jenne, Bordley, Peter, Crowe and Oliver, (all quoted by Gifford), reported cases in which the etiologic importance of sinusitis for optic neuritis was considered as proved. The impression is gathered that most of these authors consider it one of the most important causes of this condition. Cushing goes to the opposite extreme, however, apparently doubting the rhinogenic origin of many of these cases. Oliver and Crowe (quoted by Wilmer), add this very significant sentence, however, concerning these cases: "On the other hand only a percentage of patients with infection of the sinuses have retrobulbar neuritis as a complication." In this connection, the statistics of cases with sinusitis, examined routinely for evidence of optic nerve involvement, such as enlargement of the blind spots and visual field defects, are quite significant. Markbrieiter found 70 per cent. of such a series with field defects. Bordley found enlarged blind spots in thirty-one of the 102 cases. Herrenschwand, in eighteen of 150. Beck Pillat in six of fifty-three cases of purulent sinusitis, in four of sixty-five nasal anomalies producing poor ventilation and in 85 per cent. of forty-seven normal persons. Van der Hoeve found some changes in practically all cases of posterior sinusitis. In 500 cases, Herzog found slight changes, which he considered significant of pathology in the nerve, in only 2.6 per cent. In proportion to the number of cases these definite signs were many times more frequent in acute than in chronic sinusitis. He concluded that while the slight field changes reported by some observers were probably not indicative of nerve involvement, such involvement does occur in a respectable number of cases without being noticed by the patient. While most of these defects disappear as the acute sinusitis



clears up, some nerves remain temporarily damaged and this perhaps explains a certain number of cases in which optic atrophy is discovered later.

Wilmer gives the following differentiating characteristics of the central scotomata produced by disseminated sclerosis and sinus disease. "In disseminated sclerosis there is a great variability in the scotoma. The perimeter or campimeter gives the most accurate information of the extent of the involvement of the papillo-macular fibres. In the early stages the scotoma is relative and affects particularly the perception of green and red. Later blue and white are not recognizable and the scotoma becomes absolute. There may be also irregular peripheral field contractions, as associated perineuritis may add peripheral field defects to the central changes." According to Hensen (quoted by Wilmer), "The central scotoma in disseminated sclerosis is very fleeting; in fact, disseminated sclerosis never causes a scotoma of longer than three months' duration." According to Traquair (quoted by Wilmer), "The central defects in sinus disease are not characteristic but their study is of great value from a negative standpoint in enabling one to distinguish them from tobacco amblyopia or defects from pituitary tumor."

Gifford gives two reasons why opinions as to the frequency of rhinogenic retrobulbar neuritis are so at variance. One of these is that many observers consider recovery of vision after a nasal operation as definite proof that an infected sinus was the cause of the disease, while others who have watched such cases clear up spontaneously, insist that many cases operated upon would have cleared up without this, and refuse to consider sinusitis as a cause without gross evidence of sinus disease. Another reason for confusion is the failure by one group of observers to have in mind the frequent course of multiple sclerosis, which often produces as its first symptom marked loss of vision. This may clear up completely, either with or without operation on the sinuses and no other symptom may develop for years. Often not for ten years, according to Scheerer.

Wright, O. Beck, Bordley, Oliver and Crowe have written quite extensively on the pathology of sinus disease causing retrobulbar neuritis. White (quoted by Gifford) found edema, fibrous hyperplasia and chronic inflammatory changes in the mucosa, which sometimes involved the bone. At first he believed that the inflammatory process involved the optic nerve by direct extension, but later changed his

opinion. He now considers the hematogenous route to be the almost exclusive method of infection. He considers a few cases as due to hyperplasia of the turbinates with obstruction to the ostia and resulting negative pressure within the sinuses, which favors absorption of toxins and bacteria from the blood stream. O. Beck believes that the changes found in sections of the sinus wall or turbinates should be interpreted as the result of negative pressure producing a type of inflammation which may cause damage to the optic nerve. The experiments of Bordley seem to offer evidence in the same direction. Oliver and Crowe report ten cases of retrobulbar neuritis that apparently developed as a result of infection in the accessory nasal sinuses. In each of their cases a careful diagnostic study was carried out to eliminate the other common causes of retrobulbar neuritis. The nasal tissue removed was carefully examined, microscopically, in each case. While a few showed gross nasal pathology, in many no discharge or polypi were to be seen and roentgen rays were negative. These latter, however, did show on section, infiltration of the mucosa and submucosa with eosinophils and plasma cells. Bony changes were not described and evidently the bone was not sectioned in most cases. Cases which came to autopsy, reported by Redslob and Ten Doesselaere showed definite extension of inflammation from a purulent sphenoiditis through the bone to the optic nerve. These cases all seem to offer proof of direct extension through the bony wall of an infected sinus.

Herzog has tried to show that direct extension of the inflammation from sinus to nerve may occur in cases showing negative roentgen ray and nasal findings. He first studied the normal histology of the ethmoid and sphenoid bones, and described the intimate relationship between the dural sheath of the nerve and the cortical spaces of the bone, separating it from the ethmoid and sphenoid cells. He found all stages between a type with dense bone having few cortical spaces and a less common type with thin cancellous bone, whose cortical spaces offer free communication between the submucosa of the ethmoid and the nerve sheaths, which form its periosteum and sends processes directly through these cortical spaces to the submucosa. He believes the rarity of this type accounts for the rarity of optic neuritis in comparison with the frequency of sinusitis. Wilmer has presented sections from two autopsy cases, to show the difference in the relation of the nerve to the paranasal sinuses in different persons and in

different portions of the optic nerve. Meller and Nnemann believe that the slight temporary nasal inflammations following coryza are more likely to produce optic neuritis than is chronic sinusitis with the production of polypi and other gross nasal changes.

Much confusion exists in regard to the question of operation on sinuses which are only suspicious, in the presence of retrobulbar neuritis. It is universally admitted that multiple sclerosis accounts for 50 per cent. or more of these cases. If there are no neurological signs of this condition and no evidence of brain tumor or tobacco or alcohol amblyopia, the sinuses, if infected, must be treated promptly. According to Oliver and Crowe, "The edema and cellular infiltration of the nerve trunk may result in absolute blindness, as the inflammation progresses. Vision may return to normal as the edema in the nerve subsides or may only improve temporarily, regression occur, and blindness become permanent, owing to secondary optic atrophy. The duration of the inflammatory process in the nerve is of prime importance, and although a thorough diagnostic study of the patient is necessary, no time should be lost in opening the posterior group of sinuses, if they are infected." In the 15-20 per cent. of cases with negative nasal and roentgen ray findings and no other apparent cause, waiting a week or longer would seem to be accepted by most authorities as proper, since it is during this time that many begin to improve spontaneously, while waiting. Gifford advises that the various other therapeutic measures which have been credited with good results, such as sweats, foreign protein injections, ephedrin nasal sprays, or the application of adrenalin gauze packs to the ethmoidal and sphenoidal ostia should be tried. Herzog believes that where failure of vision occurs after a primary improvement with these conservative methods, opening the sinuses or improving their ventilation by turbinectomy is indicated.

When no improvement occurs under general and local treatment, Gifford believes that the time to wait before considering exploratory operation should vary according to the degree of visual defect. If the visual defect is great and blindness is threatened, he agrees with most ophthalmologists that operation is advisable after a week of observation or even sooner. White believes that 50 per cent. of cases recover spontaneously, 30 per cent. require submucous resection or turbinectomy while about 20 per cent. require free opening of the

ethmoidal and sphenoidal cells. McKenty states: "Sinusitis is never strictly confined to a single sinus and chronic sinusitis is rarely unilateral. At least to some degree, all the sinuses on the same side are affected. The anterior ethmoids and frontals rarely cause eye complications if we except direct extension of pus into the orbital fossae. The danger zone for the optic nerve and for the eye ball is in the posterior ethmoid and sphenoid regions. Clinically we observe greater toxicity here, both in a regional and in a general sense. Maxillary sinusitis of dental origin is prone to affect the eye but a maxillary involvement, as a part of a pansinusitis, is much less active in that respect."

In last analysis, quoting James A. Babbitt, the problem of greatest interest in this subject is, to determine the intranasal conditions, temporary or permanent, which contribute to pathological manifestations in the optic tract, and the manner of dealing with them most successfully. From the ocular standpoint this involves utmost precision in diagnosis; from the rhinogenic, after the diagnosis, avoidance of needless and completeness of justifiable surgery.

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# PROGRESS IN OTOLARYNGOLOGY

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AN ATTEMPT is made in the following pages to review the progress made during the past year in the field of otolaryngology, with special reference to those advances which appear to be of value in general medical practice. For the sake of simplicity, the various topics of interest will be considered separately under the appropriate headings.

## BOOKS

Three books were issued during the year with more than general interest to the practitioner. The third edition of Turner's<sup>1</sup> "Nose, Throat, and Ear" is a very helpful book because of its brevity, conciseness, and readability. The main addition to the second edition deals with "Peroral Endoscopy." The illustrations are still above the average and many are in color.

The second important book is David T. Smith's<sup>2</sup> "Fuso-spirochetal Disease." This book is of special interest because of the recent progress made in that field. This monograph includes historical sketches of the fusospirochetal diseases and a bibliography of eight hundred references to the literature.

The general practitioner will find this book of immense value both in the clinic and in the laboratory. All of the fusospirochetal organisms are enumerated and their characteristics are very clearly discussed. The illustrations are plentiful as well as truly representative. The book is divided into chapters, each describing one clinical entity; such as Vincent's angina, noma, trench mouth, pyorrhea, Ludwig's angina, pulmonary abscess, and bronchiectasis. Experimental reproduction of each disease in animals is also described. Among the thirty-two chapters there is one included on the technique of injection of iodized oils into the tracheobronchial tree.

The treatment of the fusospirochetal diseases is well covered. It is evident that Smith feels that absence of vitamins A, B, C and D lowers in many cases the resistance of the patient to fusospirochetal infections. The use of cod liver oil or its derivatives; the use of the

juices of oranges, tomatoes, and other fruits, and the use of milk and butter, are stressed in conjunction with arsenical therapy. The arsenicals are applied locally, injected intramuscularly or intravenously, depending on the individual requirements in each case. Altogether, the book is interesting, well written, and furnishes valuable information.

The most recent book on diseases of the ear is that by Watkyn-Thomas and Yates,<sup>25</sup> called "Principles and Practice of Otology." This book furnishes the most complete and up to date material at hand, and is very clear in its explanations of the topics discussed. The interpretation of vestibular function is improved by the numerous helpful illustrations. The late developments in such subjects as otosclerosis and surgery of the ear are well covered. Many original drawings and diagrams are clever and unique, and add much to the attractiveness of the presentations.

#### ANESTHESIA

Flagg<sup>3</sup> has reported his observations on four years' practice of intratracheal anesthesia. He advises such procedure in all operations, especially those upon the head and neck. His method involves the usual induction under gas-oxygen anesthesia, followed by ether and the insertion of a mouth gag. At this point, his especially devised laryngoscope is inserted. (This laryngoscope resembles an ordinary hand flash light with the usual laryngoscope blade attached at the distal end.) The epiglottis is lifted up, the glottis exposed, and a chromium plated inhalation tube is inserted into the trachea. The procedure is, therefore, somewhat similar to direct intubation.

The greatest claim made by Flagg for his method of anesthesia is the elimination of the possible aspiration of foreign materials—especially the secretions in the pharynx, which are always present during prolonged anesthesia. Other features claimed are "furnishing equipment for artificial respiration in case of respiratory failure," and increasing the margin of safety for the patient. The latter is brought about by the rebreathing which actually decreases the total amount of anesthetic (usually ether) required during an operation.

The discussion of local anesthesia in tonsil operations still continues to be interesting. Used for many years in other surgical procedures, 1 per cent. quinine and urea hydrochloride solution has been used by Trotter<sup>4</sup> in five hundred cases (2.5 cc. to each tonsil). He

injects the solution at only one point on each side—the lower third of the anterior pillar. This places the solution into the tonsillo-pharyngeal bundle and the resulting anesthesia is said to be excellent. By addition of epinephrine to the solution, vasoconstriction is obtained. Anesthesia is said to last for several days, which is, of course, of importance for the postoperative comfort of the patient.

A new drug, called Euphagin, capable of inducing local anesthesia, has been placed on the market. The anesthetic principle is amidobenzoicethylester. Laszlo<sup>12</sup> has highly recommended Euphagin for the controlling of pain following tonsillectomy. The tablets are dissolved in water and the solution allowed to trickle into the fossae. Anesthesia is said to last an hour or more. The drug is described as non-toxic and can be used in bronchoscopic and esophagosopic work. Robinson<sup>13</sup> has written that Euphagin has been used with excellent results in controlling the pain of intraoral cancer.

Still another new anesthetic is called Pantocain. It, also, is especially recommended for ophthalmological and otolaryngological practice. A 1 per cent. solution is equivalent in action to 20 per cent. cocaine applied on the mucosal surface and 2 per cent. procaine injected. It is described as being much less toxic when injected than procaine, and practically non-toxic when locally applied. Wilmer and Paton<sup>11</sup> reported a large series of successful cases in ophthalmological work in which this anesthetic was used. They approved of the solution because of its quickness of action, depth of penetration, freedom of smarting or irritation, and its inexpensiveness.

From the anesthesia standpoint, "Status Lymphaticus" is still a scourge. Various explanations of the condition have been brought out in the past—yet none definitely proved. Campbell<sup>5</sup> has reviewed the situation and reports his belief in the hypoactivity of the adrenal glands as the cause. It has been found that histamine detects individuals having "Status Lymphaticus," and he has promised to report further observations and investigations. He foresees rather soon a specific cure for the condition by the administration of some type of adrenal cortex extract.

#### DRUGS

Since ephedrine sulphate and ephedrine hydrochloride have been adopted so universally in the treatment of coryza, acute sinusitis, and

asthma, it is interesting to hear reports of unfavorable results from their use. Balyeat and Rinkel<sup>6</sup> refer to previous reports of urinary retention due to oral intake of ephedrine, and also cite cases under their observation. Constipation, due to inability to relax the sphincter ani, also was described in one patient. The bladder musculature is thought to be relaxed, and the bladder sphincter contracted, by prolonged use of the drug. These observations brought out one practical point—the trial of large doses of ephedrine orally in cases of nocturnal enuresis.

The effect of ephedrine on the nasal mucous membranes has been previously studied. It was found to be less irritating than epinephrine over long periods of administration. Stark<sup>7</sup> has reported from his studies of the nasal mucosa of rabbits that there is no apparent harm from the prolonged use of ephedrine, other than the reduction of the total amount of mucus secreted. This is, of course, probably the rationale for its use. His experiments are interesting in that 75 per cent. of rabbits whose noses were irrigated with saline developed sinusitis; of those treated with mineral oil, only 10 per cent. developed sinusitis while those treated with ephedrine were perfectly free of sinus infections.

Duke<sup>10</sup> has reviewed American literature and recalls the fact that ephedrine in a few cases has actually caused allergic symptoms to appear—in most cases a dermatitis. The allergic reaction is similar to that seen sometimes following the use of epinephrin.

#### DIET

In recent years the dietary deficiencies have been proved to be the source of many otolaryngological complaints. Cody<sup>8</sup> has summarized quite well the effects on the ear, nose and throat, of vitamin deficiencies, especially of vitamins A, D, B, and G. He refers to his rat experiments whereby it was proved that vitamin A is necessary to prevent replacement of columnar epithelium in the nose by squamous epithelium. Thus, a normal condition of the nasal mucous membrane is maintained. Head colds are decreased in number and severity, sensation of smell is preserved, sinusitis prevented. The aural mucosa is affected in a similar manner to the nasal mucosa if vitamin A is deficient, with a resultant deafness together with other aural symptoms. Vitamin G deficiency has no effect on the ears,



nose, or throat; and vitamin D was not shown by him to have any special effect on the ears, nose, and throat. When there is a vitamin B deficiency, there is an overactivity of the mucous membrane, with symptoms of nasal discharge and obstruction, together with a definite clinical thickening of the mucous membranes.

Smith,<sup>2</sup> in his "Fuso-spirochetal Disease," refers frequently to avitaminosis, or at least deficiencies, as large factors in the severity of the diseases he describes, and insists on an adequate and well-balanced diet in his treatment of these diseases. The diet is to be used in conjunction with the arsenicals.

Ullmann<sup>14</sup> has treated a series of chronic sinus infections by the dietary elimination of sodium chloride. He discusses rather briefly, but fully, the sodium chloride metabolism in the body. His patients were placed on a vegetable diet with raw and cooked fruits, the diet being followed strictly for a week or thereabouts. He thought he noticed improvement locally in the nose of the patients, and stated that his patients themselves had noticed improvement. Gradually, the patients were allowed to go back to their usual diet, with the exception of one day each week, which was set aside for his dietary regime. He insists that the urine be neutral in character, and regulates the diet by the weekly determination of the pH and chlorides. Cod liver oil is used as a dietary adjunct. All of his patients had chronic sinusitis, were free of allergy, and had not been relieved by surgical operations. A few of his patients had been operated upon several times.

#### LABORATORY

The Schilling test—the differential blood count which became popular several years ago is more universally used than ever. The fact that some otolaryngological conditions are quite obscure in their daily progress makes the Schilling count very useful. With the shifts to the left or right, varying according to whether the patient is improving or not, one is able to keep up with the actual condition of the patient in a manner not demonstrated by other clinical methods. The acute mastoid infections, septicemias, acute sinus infections, acute pharyngeal infections and other acute diseases have been mentioned as being most intelligently followed by the Schilling count. An accurate prognosis is available in each case.

## EQUIPMENT

One wonders frequently what is the exact status of electrosurgery. There is evidently not the same general enthusiasm of several years ago; especially not in the otolaryngological field. There is, however, considerable enthusiasm manifested by some for its restricted use in this specialized field. Balmer,<sup>9</sup> working under a grant from the American Medical Association, has summarized his findings as follows: "(a) Electrosurgery is a valuable aid to surgery. (b) A thorough knowledge of the physics of the electrical current is absolutely necessary for its use with safety. (c) There is the need for considerable knowledge of the great selectivity of currents in order to use the proper current in any selected case. (d) Electrocoagulation does not replace surgery in the removal of tonsils except in certain selected cases. The selected cases are enumerated as follows: tonsillar stumps or lymphoid hypertrophies and regeneration; lingual lymphoid hypertrophies; fungous diseases of the tonsils; blood dyscrasias (hemophilia and anemias); general systemic conditions involving a serious danger of the heart, lungs, or kidneys; the aged and infirm, and those who absolutely refuse surgical removal."

Balmer reports a procedure that he has found satisfactory in the use of electrosurgery—the removal of only the cryptic portion of the tonsil. This is done by a few treatments of the tissue between the crypts, leaving the basic portion of the tonsil intact. He terms the procedure "diathermo-cryptectomy." He recommends such procedure for singers or anyone concerned about the postoperative effect on the voice.

Hollander<sup>10</sup> has reported practically the same results as the above in his summary of his investigations regarding tonsillectomy by the electrosurgical method. Thus it appears that the status of diathermy for the removal of tonsils is more or less definitely established. At least limitations have been put to its use.

## ALLERGY

Eczema in childhood has been brought up for discussion once again, and is here mentioned simply because the local affections in the ear, nose, and throat are not held responsible. The focal infection theory has been supplanted by the allergy theory. Bivings<sup>15</sup>

contends that most infantile eczemas are allergic in origin and that offending foods are primarily the causative agents. He states that by their limitation, prompt and lasting relief can be obtained. He finds that cow's milk, eggs, and wheat (whole) are the main foods at fault. Also of interest is that the onset of eczema occurs about the same time that the above mentioned foods are added to the infant's diet.

Gelfand<sup>16</sup> and Brown<sup>17</sup> brought again to our attention some of the important factors in allergic study. Brown feels that a thorough history should indicate to some extent what tests are necessary, since many useless ones are made. He does insist, however, that routine tests be made with the following: animal epidermals, horse dander, cat hair, dog hair, rabbit hair, cattle hair, chicken and goose feathers, and sheep's wool. Foods: wheat (whole), egg, and cow's milk. Miscellaneous: orris root, house dust, cottonseed, linseed meal and horse serum. Bacteria: *Staphylococcus pyogenes aureus*, *Staphylococcus pyogenes citrius*, *Streptococcus haemolyticus*, *Streptococcus viridans* and *Micrococcus catarrhalis*. Pollens: short and giant ragweed, timothy, orchard grass, English plantain, roses and mugwort.

He cites the importance of the calcium and phosphorus studies of the blood, blood sugar determinations, and the percentage of eosinophiles in the differential blood count. The basal metabolic rate is always an important study. Further investigations include the mucous membrane (intranasal and conjunctival) reactions and otolaryngological examination. The treatment recommended is: palliative locally in the nose with bland non-irritating solutions to form a film of protection to the mucous membrane from the offending cause. Plain mineral oil fulfills this requirement very aptly. Curative treatment, of course, implies desensitizing injections and elimination of the offending materials. Gelfand refers to several technical faults that may be responsible for some of the failures noticed in practice. The chief causes of failure he ascribes to inadequate or improper therapy, questionable potency of unpreserved solutions, inability of the patient to develop tolerance to the extract and failure to combine preseasonal with coseasonal therapy. The importance of recognizing the individual features of each case, with modification of therapy to the individual needs, is stressed.

From the surgical viewpoint, Mullin<sup>18</sup> points out the inadvisability of performing operations intranasally until desensitization

has occurred. His reason for this is the tendency for the newly formed mucosa to assume an allergic appearance and function.

Duke<sup>19</sup> has written a careful and elaborate review of the progress made in allergic fields during the past year in relation to otolaryngology. The article is most heartily recommended for reference. Since the article itself is a review, it will here suffice to mention only a few of the outstanding points. He reports the discovery of new agents as causative factors of allergy, cites the progress made in the study of fungi as related to allergy, and the effect of oily substances of plant origin as the cause of dermatitis, and finally discusses the newer conditions which are grouped under the term "physical allergy."

Smith<sup>20</sup> has given an interesting detailed study of several hundred cases of asthma. He found chronic bronchitis a common complaint in both the extrinsic and intrinsic types of asthma. Hay fever was associated with the extrinsic type only. Infected tonsils, he thought, although present, played a minor role, if any part, in the disease.

Mullen<sup>21</sup> finds that a large percentage (about 16 per cent.) of cases with paroxysmal asthmatic attacks show no evidence of allergic disease or sinus infection. He explains the condition as a nerve reflex imparting undue stimulation to the vagus nerve and the sympathetic nervous system.

#### ROENTGEN RAY

Sussmann<sup>22</sup> suggests, as has Pancoast,<sup>23</sup> the fluoroscopic and roentgenologic examinations of the neck in the study of diseases of the throat. The greatest benefits derived thereby are localizations of pharyngeal and laryngeal abscesses, foreign bodies, delicate studies of how extensive infections of these regions may be, the outlining of tumors, stenoses and traumatic conditions.

Persistent nose bleeds of severity have been treated by Seal<sup>24</sup> with radium. Over one hundred cases have been treated by this method after all other methods of therapy failed. Radium is applied over the anterior portion of septum (Kiesselbach's area). A few days after the radiation, dry crusting occurs over the treated area. But this, in all cases, was most satisfactory to the patient, compared to the continued nose bleeds. Absolute cure was reported in all cases.

## FOCAL INFECTIONS

Richards<sup>26</sup> recalls to attention the probable bacteremia produced by massage or irritation of tissues containing focal infections. He demonstrated in eighty cases, that by massage for five minutes with the finger, of chronically infected tonsils, bacteremia was produced in eighteen cases if a blood culture was made immediately following the procedure. The blood culture was still positive after one hour in six of these cases. All cases showed streptococci in throat cultures previous to the procedure. Massage of involved joints for ten minutes in two hundred and sixty cases, produced a positive blood culture in twenty-three cases immediately thereafter, and in one case after one hour had elapsed. Similar results were obtained on massage of the prostate, infected gums and furuncles. For several days, there are local and generalized reactions following the manipulation in some of the arthritic patients. Chills occurred in two patients following tonsillar massage. He promises a later report of studies in strictly arthritic patients.

Pilot<sup>27</sup> observed arthritis (rheumatic type) and arthralgia developing in patients several weeks after apparent recovery from severe sore throats due to the *Streptococcus epidemicus*. In some instances, the tonsils had been removed. In those cases, when the throat cultures for *Streptococcus epidemicus* became negative, the arthritic symptoms disappeared. Similarly, in patients whose tonsils showed the epidemicus organism, arthritic symptoms disappeared after the removal of the tonsils. It is pointed out that the organisms do not always penetrate into the tonsillar tissues to cause symptoms, since microscopically it was found in many cases that the infection was entirely restricted to the crypts. Hypersensitivity to any new types of infection is also considered the cause of arthritis.

It is stated that *Streptococcus epidemicus* is found in about 1 per cent. of normal throat cultures, compared to 61 per cent. of ordinary hemolytic streptococci usually found in normal throats. However, arthritis is present in almost all of the patients with positive throat cultures for *Streptococcus epidemicus*. The differential of the *Streptococcus epidemicus* is obtained by the use of aseptic blood agar, on which large, moist, or flat colonies will be found. In wet preparations, encapsulated cocci were found when india ink was used.

Sydenham's chorea (St. Vitus Dance), which is more common in children (three times in a female to once in a male), is considered by Davis<sup>28</sup> to be due to a chronic sinus infection. Infections, such as chronically diseased tonsils, have always been considered etiological factors. Now the chronic sinus infection is added, which is probably more important than the previous list of factors. Improvement or cure is expected after clearing up, by surgery, the sinus infection. Davis reports a total of fifty-two cases of chorea and of that number, fourteen (25 per cent.) had definite paranasal sinus infection.

An obstetrical observation of import has been recorded by Williams.<sup>29</sup> Considering the fact that eight thousand women die annually in the United States of puerperal infection, he investigated what association there might be between puerperal infection and upper respiratory infections. He found the curve of incidence of puerperal infection closely following the curve of incidence of respiratory infections, but appearing at a slightly later date. The suggestion was made that in late pregnancy, the patient be strictly isolated from members of the family who have upper respiratory infections. In case of respiratory infection in the pregnant woman it is urged that she be treated immediately and thoroughly. Also, it was suggested that throat cultures be made of the family and the personnel in charge of the case. If any of them have the slightest symptoms of upper respiratory infection, the wearing of masks and other usual preventive hygienic measures are to be strictly enforced.

#### TONSILS AND ADENOIDS

In the previous paragraph, reference has been made to the association of tonsillar infections with arthritis, chorea and puerperal infections. Other literature during the year regarding our knowledge of tonsils and adenoids was not of material significance. During the latter part of the previous year, Lierle and Potter<sup>30</sup> reported that tonsillectomy and adenoidectomy in a series of diabetic children caused within one year an increased tolerance of carbohydrates in 70 per cent. of their patients.

In summarizing his study of the pathological conditions of tonsils, Rhoads<sup>31</sup> probably expressed the opinion of all conservative laryngologists when he stated that the small, smooth, fibrous tonsils or tonsillar stumps cause more systemic diseases than do the large simple hypertrophic tonsils. The bacterial count in the small tonsils

was much higher than in the larger ones. He again expressed the view that inspection of the throat, alone, does not justify tonsillectomy. The history, the complete general examination of the patient and the laboratory data are much more important. When other foci are not found to be the cause of systemic disorder, tonsillectomy is then justifiable.

An interesting table of eight hundred and seven pairs of tonsils removed showed six hundred and five cases of hypertrophic tonsils; probably the most of them in children. Five hundred and eighty of the total showed ulcers in the crypts extending into the tonsillar tissue. The small fibrous tonsils were found in one hundred and fifty-five cases.

A study of adenoids in an effort to determine the frequency and severity of upper respiratory infections in three hundred and seventeen adults was made by Gafafer.<sup>32</sup> Of the total, two hundred and thirty-five had adenoids and eighty-two had no adenoids. There was no difference found in the frequency, severity, or types of upper respiratory infections in comparing the two groups during an observation period of more than thirty-five weeks.

Carpenter and Boak<sup>33</sup> have found *Brucella abortus* (the organism of undulant fever) in eight of fifty-six pairs of tonsils. Their work in Rochester, New York, indicated that milk was probably the source of the infection. They mention the work of two other groups doing similar investigations, one in Maryland and the other in upper New York state. In New York state, no *Brucella* organisms could be found in forty-nine patients. In Maryland, however, two cases were reported as positive in one hundred and sixteen cases studied. The question was brought up whether *Brucella abortus* infection does not cause tonsillar and generalized lymphoid hypertrophy, since it has been shown experimentally that lymphadenopathy is one of the characteristic findings in the infection.

#### NOSE

Pratt<sup>34</sup> is certain that atrophic rhinitis (adrenalism. Pratt feels that the atrophy of the one of the maxillary sinuses of the subnormal glands. He rarely has explained this but usually

active adrenals. It was also pointed out that all negroes have very wide nasal spaces.

The onset of the disease is ascribed to a shock of varied types to the general system; such as produced by the acute infections, pregnancy, childbirth, etc. If another shock later occurs, a stimulation back into normal function of the glands may occur, and he feels that recovery from atrophic rhinitis occasionally comes about in just such manner.

The treatment recommended by Pratt is the oral administration of suprarenal glandular tissue. Two grain tablets, three times daily with meals, are prescribed over a period of several months. General palliative and local therapy may also be employed. Cures are reported by him—the odor disappearing in a week or so and the crusts at a slightly later date.

Szalka<sup>35</sup> holds to the prevalent idea that abnormally large breathing space and avitaminosis are the causative factors of the disease.

Pratt<sup>34</sup> and Birkholz<sup>36</sup> both are certain that hypertrophic rhinitis does not precede atrophic rhinitis.

Bernheimer<sup>37</sup> reviewed atrophic rhinitis from the toxoid therapy standpoint and found the therapy to be of no value. Diphtheria and pseudodiphtheria organisms were found in the nasal cavity of many patients having atrophic rhinitis. These patients were treated with a vaccine of the toxoid with no benefit to the patient. He does not approve of organotherapy unless a definite deficiency of a certain gland can be demonstrated. Reference is made to the work of Malherbe, reported in 1927, who believed that the pseudodiphtheria bacillus liberated toxins which affected the endocrine glands. As an example he felt that women had an increased amount of symptoms locally in the nose during menstruation—indicating ovarian involvement. Bernheimer more or less admits that hypofunction of the endocrine glands may play a part but is more interested in the effect of pseudodiphtheria bacilli. He was disappointed when he was unable to reproduce atrophic rhinitis in experiments on rabbits.

Proetz<sup>38</sup> and Hilding<sup>39</sup> have published observations on the physiology of the normal mucous membrane of the nasal passages. The delicate ciliary action in the nose and the air currents are elaborately described. They show that the work that can be performed by the ciliated epithelium is much more than was previously suspected. The ease with which irritating solutions, sprays, toxins, etc., embarrass



the cilia is mentioned because of the complications that may follow. Sinusitis is the most frequent of these.

Vasomotor rhinitis, both of allergic and non-allergic etiology, can be controlled by alcoholic injection of the sphenopalatine ganglion according to Walsh.<sup>40</sup> In a series of ninety cases it was found that the effect of the injection lasted over a year in 30 per cent. of the cases, up to one year in 30 per cent. and up to six months in 30 per cent. of the cases. Failure was reported in 9 per cent. and these failures were explained as being due probably to faulty technique. The allergic type is best treated by protein therapy, whereas the non-allergic type is especially benefited by sphenopalatine ganglion injections. It is frankly stated that swelling of the eyelids or of the cheeks, headache, and other phenomena, are not uncommon sequels. In a short period of time, however, all of these complications completely clear up.

Beck and Guttman<sup>41</sup> have found two new types of malignant epithelial neoplasm of the nasopharynx. They are named lympho-epithelioma and transitional cell carcinoma. They have early metastases and are best treated with radium since they are extremely radio sensitive. The same authors<sup>42</sup> have reviewed the malignant tumors of the nose and those of the paranasal sinuses, and have described the varied treatments for such neoplasms. The use of surgery, electrosurgery, roentgen ray, and radium is covered.

Pneumococcus membranous nasopharyngitis is now recognized as a clinical entity and case reports are becoming more numerous. Fox<sup>43</sup> states that the patients (always children) have high fever, a membrane in the nose and nasopharynx, and that the patients very early become dehydrated and are very subject to complications. The disease is differentiated from diphtheria, spirochetal infection, agranulocytic angina and other infections only by the actual identification of the pneumococcus. Treatment consists of maintaining the fluid intake and the use of ethyl hydrocupreine sulphate locally.

#### PARANASAL SINUSES

The paranasal sinuses still offer the opportunity to write volumes upon their anatomy, physiology, pathology, symptomatology and treatment. Very little new material of clinical value has been produced. Some important facts, however, have been brought out. Smyth and Fred<sup>44</sup> are to be commended for a compilation of the

previous year's published reports, which are detailed reports but necessarily brief. Naturally, in this summary, there is an abundance of new clinical facts. More than two hundred articles are summarized giving academic as well as clinical observations.

Ellis<sup>45</sup> is very enthusiastic about the treatment of the donlonrenx (trifacial neuralgia), by removing mucous polyps from the maxillary sinus of the affected side. He reports eight cases, followed for only a short postoperative period, in which the examinations including roentgen rays failed to demonstrate pathological change, but all showed at operation, or later in microscopic sections, diseased tissue. The operations were partially window resections and partially Caldwell-Luc operations. He feels that bony dehiscences and other anatomical abnormalities cause exposure of some of the branches of the fifth nerve, which in turn allows the symptom complex of the disease to develop.

Shea<sup>46</sup> recalls in his paper before the Southern Medical Association, that the paranasal sinuses play a great part in the auto-immunization of the patient. He feels that a handicap is imposed upon this performance when the tonsils are removed in very young children. This is suggested by casual reference to the familiar Waldeyer Ring of defense. In case of any weakness in the immunity, he suggests the stimulation of this immunity by the use of vaccines, nonspecific protein therapy and the vitamins.

Much is written about the pulmonary complications of sinus infections. Smith<sup>2</sup> feels that since fusospirochetal organisms are not often found in the sinuses, they are not directly responsible for bronchiectasis. He explains the condition in the following manner: that a chronic sinusitis produces a chronic bronchitis, which in turn makes a fertile field for the implantation of the fusospirochetal organisms. The mouth is the point of origin of the latter organisms.

Vail<sup>47</sup> denotes a syndrome of nasal neuralgia with its extension into the face, head, neck and shoulder as Vidian neuralgia. The condition, named by Sluder "sphenopalatine ganglion neuralgia," causes similar symptoms with extreme pain behind the ear and at times down the arm and fingers. Vail thinks the symptoms of both conditions are due to an irritation or inflammation of the Vidian nerve, and are not due to any affection of the sphenopalatine ganglion. He always finds a sphenoid sinus infection present and his treatment is naturally to eradicate the infection.

The malignant growths of the sinuses were discussed in several papers last year. Perhaps the most interesting is that of Dupuy.<sup>48</sup> In a series of sixteen cases, resection of the maxilla was done. The patients were anesthetized with intravenous sodium amytal. A tracheotomy was done to prevent lung complications, the tube being removed at about the fifth postoperative day. Radium was applied after operation. Metastases were found to occur late, and recurrence was noted in only one patient, a child with extensive sarcoma. The tumors were found in all sixteen cases to be of dental origin. Fourteen of these patients were living from one to three years later. Dental and maxillary plates were supplied after the maxillary resection to close over the remaining defect.

#### PHARYNX

In conjunction with the cases of pneumococcus membranous nasopharyngitis in children, described (*vide supra*) by Fox,<sup>43</sup> we have an interesting report of a similar disease in adults, except that the disease is confined locally to the pharynx. Richey<sup>49</sup> reports five cases. There was a history of previous attacks in three of the patients, and even after tonsillectomy there were recurrent attacks in one instance. The leukocyte count varied from six thousand to nine thousand and five hundred and the temperature from 100 to 103°F. The main complaints were extreme pain in the throat, dysphagia and cervical adenitis. Therapy, in the adult cases of Richey, was not successful until topical applications of ethyl hydrocupreine hydrochloride were made. This is of interest mainly because Fox had obtained the same results in children. Bacteriological examinations alone can make the diagnosis certain.

Houser<sup>50</sup> has studied the anatomy involved in Ludwig's angina. He found the reason for the sublingual swelling to be the tenseness of the mylohyoid muscles and of the deep cervical fascia. Edema of the larynx in these cases is due to the proximity of the larynx to the actual inflammatory tumor (two and a half inches in the adult). He suggests trying the sublingual method of drainage before resorting to external drainage. Dental caries was found to be the most common cause of the fifteen cases he reported. Staphylococci and streptococci were the bacteriological agents reported in four cases while no organism was reported in the other eleven cases. Smith<sup>2</sup> states that when foul pus and gangrene is found in Ludwig's angina, it is due to the

effect of the fusospirochetal organisms. He agrees that the condition may be due to streptococci or staphylococci without fusospirochetal organisms. Smith advises intravenous injections of arsenic as soon as the diagnosis is made, this to be followed by radical surgery and this in turn by more arsenic intravenously. Houser failed to mention in his paper, that spirochetes are associated with Ludwig's angina. He also failed to mention the use of arsenical therapy in this disease.

The newest observations upon agranulocytic angina have been published by Harkins.<sup>51</sup> He considers the disease to be a true primary granulopenia. He concludes that the oral lesions are secondary to the granulopenia. This view had already been accepted. The etiological factor, he thinks, may be a congenital deficiency of the bone marrow, an allergic state, an endocrine disturbance, chemical poisoning or some unknown bacterial infection. Summarizing the treatment of the disease, he states that oral antiseptics merely delay the invasion of tissue by the organisms, that blood transfusions and roentgen ray therapy are of no proved value and that methods to stimulate the bone marrow have been ineffectual with one exception. This exception is nucleotide which in some cases has been beneficial.

Beck and Guttman<sup>52</sup> find that surgical removal of malignant growths in the posterior third of the tongue is unsuccessful. The application of radium has reduced the recurrence of growths in this particular area until it is now found in only 30 per cent. to 40 per cent. of the cases. The method of choice in treating malignant growths on the posterior third of the tongue is the use of the telio-radium bomb. Surgery is still indicated for small growths located on the anterior third of the tongue.

#### LARYNX

During the year 1930, there were one hundred and ninety-eight deaths in New York City from diphtheria. Of this number only two had received diphtheritic immunization. Blum<sup>53</sup> has been studying immunity produced in infants and finds that the greatest effect occurs during the ages from two to four years. There is very little immunity produced from birth up to three months of age. He advocates that Schick tests be made on all infants below nine months of age before immunization. After immunization Schick tests should always be done within three to six months after.

Diphtheria is decreasing in the larger cities. In the ninety-one largest cities of the United States, the death rate for the year 1931 was 3.72 per one hundred thousand. During 1930 the rate was 5.12.<sup>54</sup>

The non-diphtheritic infections of the larynx, trachea and bronchi are reported more frequently. The reason is that symptomatic diseases of this area have been found not to be true diphtheria. The mortality rate in non-diphtheritic infections of these organs is higher than in diphtheria. The crusts from the thick discharge that forms in the tracheobronchial tree are more difficult to treat. Diphtheria antitoxin administered early in the disease naturally gives no beneficial results. The organisms found are usually streptococci, staphylococci, pneumococci and influenza bacilli. The treatment of choice is tracheotomy. Thick tenacious discharge is commonly found in the trachea at operation. Gittins<sup>55</sup> has reviewed the previous literature and reports twenty-four cases he has observed. The mortality rate in his series was 37 per cent.

Tracheotomy is often preferable to intubation to relieve dyspnea. A study has been made by Richards and Glenn<sup>56</sup> of the wound and scar following tracheotomy. They find that tracheotomy wounds usually heal by connective tissue filling in the cartilaginous opening, and that internally the wound is covered by a slightly altered, but still functioning, epithelium. No granulations or mechanical obstructions were observed experimentally. These findings are of importance when one considers the irritation or compression necrosis with a subsequent stenosis found occasionally following intubation.

Tucker<sup>59</sup> also states that in infants tracheotomy preserves the laryngeal structures better than intubation.

Text books for years have taught that a paralyzed vocal cord assumes the "cadaveric position." This position is one between that of quiet respiration and phonation. New and Childrey<sup>57</sup> state that the cadaveric position is never permanently assumed; that the vocal cord found in the midline following an injury to the recurrent laryngeal nerve either returns to its normal function or remains in the midline, and, furthermore, that vocal cords found in the cadaveric position shortly after injury either return to normal function or assume midline position. Clinically these facts are important since respiration would not be impaired if bilateral cadaveric positions

were assumed, but tracheotomy or other surgical procedure would be necessary after the midline was assumed by both vocal cords.

Wilkinson<sup>58</sup> has presented a good review of laryngeal tuberculosis. Numerous excellent references are given. Nothing new clinically is offered in his review, but the practitioner is requested to see that his tuberculous patient has frequent laryngeal examinations. Treatment may be instituted at once if laryngeal tuberculosis should develop. He mentions that electrocauterization still commands the greatest use in the treatment of laryngeal tuberculosis.

Graham,<sup>60</sup> in reviewing laryngeal carcinoma, found a positive "Haffner Beeverman test" in some of his early cases. This test is said to demonstrate an active epithelial tissue proliferation by virtue of an indole urinary reaction. In his cases the reaction became negative after the malignancy had been removed. Graham has faith in the test, since it has been accurate in 93 per cent. of two thousand cases of definitely proved carcinomata. The malignant growths were located in different parts of the body.

Tucker<sup>61</sup> once more calls attention to hoarseness as significant of malignancy. Biopsy is necessary for the sure diagnosis. Many cases can be cured by the laryngofissure operation.

Numerous articles dealing with bronchial and esophageal affections appeared in the literature of 1932. Foreign bodies in the bronchial tree or esophagus with the complications that followed and the difficulties encountered in their removal are frequently reported. The various pulmonary suppurations have been thoroughly reviewed in the recent literature. Reports of pulmonary blastomycosis and other unusual pulmonary affections are found. Reviewing the entire work it suffices to say that nothing new of clinical importance has been brought out.

Interesting observations upon various esophageal and pulmonary diseases and the methods of treating them were presented at the American Bronchoscopic Society.<sup>62</sup> New instruments were demonstrated. Realizing that these articles are of more interest to the specialist in bronchoscopy and esophagoscopy than to the internist or practitioner further mention of them need not be made.

#### EAR

Affections of the middle and internal ear have aroused much interest during the last few years. A vast amount of research has

been directed towards finding a means to combat deafness. Otitis media with its sequels and complications has been widely studied. Crowe and Hughson<sup>63</sup> have continued their cat experiments, demonstrating that when cotton or other materials are placed against the round window the intensity of voices passing through the hearing apparatus is increased. In their latest experiments a fascial graft was placed over the round window which readily grew. The results are the same as were obtained in the use of cotton. A large series of experiments have demonstrated invariably improved reception. The experiments were very carefully checked and an elaborate technique was employed. The clinical application of these experiments may soon appear in an actual operative procedure to improve the hearing of deaf patients.

Crowe had previously shown<sup>64</sup> the results obtained on severing the tensor tympani muscle or increasing the tension of the muscle. On severing that muscle there is a loss of hearing for high tones and this loss can be restored by the fascial grafts above mentioned. There certainly appears to be a happy clinical application in store for the researches of Crowe and his co-workers.

Gottlieb<sup>65</sup> publishes further observations upon the syndrome which he terms "auro-hepatico-pancreatic syndrome." In this category he includes a group of patients with tinnitus, impaired hearing, vertigo, headache and blurred vision. There are also gastro-intestinal symptoms, flatulence, belching, fulness and discomfort after eating with more often constipation than diarrhea. A generalized feeling of fatigue is always present. He states that in all these patients he finds a low basal metabolic rate, elevation in the number of small lymphocytes, increased indican in the urine, and decreased cholesterol and bile pigments in the duodenal fluid. Pancreatic ferments are also decreased. A fairly large group of patients is recorded together with the treatment used and its results. It is claimed that improvement in hearing follows the hepatico-pancreatic therapy. It is remarked that hearing did not become worse in a single patient while under observation.

In reviewing the bibliography of the previous year on otitis media and lateral sinus thrombosis, Kopetzky<sup>66</sup> finds two equally divided groups, one advising ligation of the jugular vein, the other advising against it. He personally takes the middle ground and feels that

each individual case is a separate problem, pointing out that the important procedure is to clean out the infection whether it be in the mastoid or in the lateral sinus. He reminds us that ligation of the jugular vein does not prevent bacteremia and toxin absorption. Potts<sup>67</sup> and his co-workers feel that jugular ligation is rather necessary and have followed this procedure in fifty-three of sixty-three cases. They report a mortality of 14 per cent. These observations extend over a period of more than twenty-five years. He suggests that in some cases instead of jugular ligation a simple packing of the lateral sinus at the proximal and distal ends suffices. The jugular vein will return to normal function upon the removal of the packs.

It has been about eight years since the view was brought out that there was an aural background for the intestinal intoxication found in infants. We still note further observations and studies on this subject. Maybaum<sup>68</sup> and others at Mt. Sinai Hospital observed thirty-nine cases of intestinal intoxication in infants and charted the aural findings daily. The final summary of the cases includes observations on the seventeen that recovered from the disease and on the twenty-two who died; postmortem findings being included. Maybaum concludes that there was no association of aural disease with the intestinal disease—a conclusion similar to the view at present accepted (which is a reversal of the opinion held some years back). Campbell,<sup>69</sup> in showing the relation of sinusitis in infants to otitis media, remarks that probably some of the gastro-intestinal symptoms of infants may be due to sinusitis.

Nothing new has come from the studies upon otosclerosis. It may be of interest to cite the varied theories of its etiology. Fowler<sup>70</sup> has briefly summarized the different opinions of Brühl, Wittmaack, Weber and Mayer. He says that Brühl believes otosclerosis is due to an irritation, that Wittmaack thinks it is due to a venous stasis, that Weber contends that it is a metabolic disease similar in most regards to osteitis fibrosa, and finally, that Mayer thinks it is the result of a fracture of some type, probably due to a strain.

Investigation is pursued in many places upon the problems of this hereditary disease. Operations are now being reported with slight success, but the future still holds as a secret the truly successful treatment.



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